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(54) Title: SUBSTITUTED PIPERAZINES, (1,4) DIASZEPINES, AND 2,5-DIAZABICYCLO (2.2.1) HEPTANES AS HISTAMINE H1 AND/OR H3 ANTAGONISTS OR HISTAMINE H3 REVERSE ANTAGONISTS

(57) Abstract: The present invention relates to novel piperazine and azepine derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurodegenerative disorders including Alzheimer's disease.

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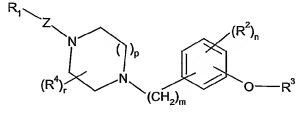
SUBSTITUTED PIPERAZINES, (1,4)DIAZEPINES, AND 2,5-DIAZABICYCLO(2.2.1)HEPTANES AS HISTAMINE H1 AND/OR H3 ANTAGONISTS OR HISTAMINE H3 REVERSE ANTAGONISTS

The present invention relates to novel piperazine and azepine derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurodegenerative disorders including Alzheimer's disease.

WO 02/76925 (Eli Lilly) describes a series of compounds which are claimed to be histamine H3 antagonists. WO 02/055496 (GlaxoSmithKline) describes a series of piperidine and piperazine derivatives which are claimed to be inducers of LDL-receptor expression. WO 02/12214 (Ortho McNeil Pharmaceutical Inc) describes a series of substituted aryloxyalkylamines which are claimed to be histamine H3 antagonists.

The histamine H3 receptor is expressed in both the mammalian central nervous system (CNS), and in peripheral tissues (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic, adrenergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel H3 antagonists and/or inverse agonists such as the current series could be useful for the treatment of cognitive impairments in neurological diseases such as Alzheimer's disease and related neurodegenerative disorders.

The present invention provides, in a first aspect, a compound of formula (I):



(I)

wherein:

R^1 represents hydrogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-

heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl,- heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl, -heterocyclyl-heterocyclyl,

wherein R^1 may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, $COOR^{15}$, cyano, -C_{1-6} alkyl-cyano, nitro, oxo, trifluoromethyl, trifluoromethoxy, fluoromethoxy, difluoromethoxy, C_{1-6} alkyl (optionally substituted by a $COOR^{15}$ group), C_{2-6} alkenyl (optionally substituted by a $COOR^{15}$ group), C_{2-6} alkynyl (optionally substituted by a $COOR^{15}$ group), C_{1-6} alkoxy (optionally substituted by a $COOR^{15}$ group), pentafluoroethyl, C_{1-6} alkoxy, C_{2-6} alkenoxy, aryl, arylC_{1-6} alkyl, -CO-aryl (optionally substituted by a halogen atom), -CO-heteroaryl, -C_{1-6} alkyl-CO-aryl, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, sulfonyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group -COR^{15}, -$NR^{15}R^{16}$, -$CONR^{15}R^{16}$, -$NR^{15}COR^{16}$, -$NR^{15}SO_2R^{16}$ or -$SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl or together may be fused to form a 5- to 7- membered non-aromatic heterocyclic ring optionally interrupted by an O or S atom and optionally substituted by a halogen, C_{1-6} alkyl or -C_{1-6} alkylC_{1-6} alkoxy group;

Z represents a bond, CO, $N(R^{10})CO$ or SO_2, such that when R^1 represents hydrogen, Z represents $NR^{10}CO$;

p is 1 or 2;

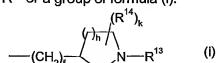
m, n and r independently represent 0, 1 or 2;

R^2 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl, such that when n represents 2, two R^2 groups may instead be linked to form a phenyl ring;

R^4 represents C_{1-6} alkyl, or when r represents 2, two R^4 groups may instead together form a bridged CH_2, $(CH_2)_2$ or $(CH_2)_3$ group;

R^{10} represents hydrogen or C_{1-6} alkyl, or R^{10}, together with the nitrogen to which it is attached and R^1 forms a nitrogen containing heterocyclic group;

R^3 represents -$(CH_2)_q$-$NR^{11}R^{12}$ or a group of formula (i):



(I)

wherein q is 2, 3 or 4;

R^{11} and R^{12} independently represent C_{1-6} alkyl or C_{3-6} cycloalkyl or together with the nitrogen atom to which they are attached represent an N-linked nitrogen containing heterocyclyl group optionally substituted by one or more R^{17} groups;

R^{13} represents hydrogen, C_{1-6} alkyl, -C_{1-6} alkyl-C_{1-6} alkoxy, C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl or heterocyclyl;
R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloalkyl, OH, diC_{1-6} alkylamino, C_{1-6} alkoxy or heterocyclyl;
f and k independently represent 0, 1 or 2;
g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;
with the proviso that when m represents 1, n and r both represent 0 and R^3 represents –$(CH_2)_3$-N-piperidine or –$(CH_2)_3$-N(ethyl)$_2$, R^1-Z represents a group other than methyl, -CO-O-C$(CH_3)_3$ or benzyl;
and with the proviso that when m, n and r all represent 0, p represents 1, R^3 represents –$(CH_2)_3$-N-pyrrolidine or –$(CH_2)_3$-N-piperidine, R^1 represents benzyl, Z represents a group other than a bond;
and with the proviso that when m, n and r all represent 0, p represents 1, R^3 represents–$(CH_2)_3$-N-piperidine, R^1 represents isopropyl, Z represents a group other than a bond;
and with the proviso that when m represents 1, n and r both represent 0, p represents 1, R^3 represents–$(CH_2)_3$-N-piperidine, R^1 represents methyl, isopropyl, aryl or benzyl, Z represents a group other than a bond;
and with the proviso that when m and n both represent 0, R^3 represents –$(CH_2)_3$-N(ethyl)$_2$, p represents 1, r represents 2 and R^1 and R^4 both represent methyl, Z represents a group other than a bond;
or a pharmaceutically acceptable salt thereof.

In one particular aspect of the present invention, there is provided a compound of formula (I) as defined above wherein:
R^1 represents a group other than hydrogen, -C_{1-6} alkoxy or -C_{1-6} alkyl-C_{3-8} cycloalkyl; and R^1 is optionally substituted by one or more substituents other than $COOR^{15}$, -C_{1-6} alkyl-cyano, C_{1-6} alkyl substituted by a $COOR^{15}$ group), C_{2-6} alkenyl (optionally substituted by a $COOR^{15}$ group), C_{2-6} alkynyl (optionally substituted by a $COOR^{15}$ group), C_{1-6} alkoxy (optionally substituted by a $COOR^{15}$ group), C_{2-6} alkenoxy, aryl, arylC_{1-6} alkyl, -CO-aryl (optionally substituted by a halogen atom), -CO-heteroaryl, -C_{1-6} alkyl-CO-aryl or C_{3-7} cycloalkyl; and
R^{15} and R^{16} independently represent a group other than C_{3-8} cycloalkyl or together may be fused to form an unsubstituted 5- to 7- membered non-aromatic heterocyclic ring optionally interrupted by an O or S atom; and
r represents 0; and
two R^2 groups are not linked to form a phenyl ring; and
R^{11} and R^{12} independently represent a group other than C_{3-8} cycloalkyl; and
R^{13} represents a group other than -C_{1-6} alkyl-C_{3-8} cycloalkyl.

In a second particular aspect of the present invention, there is provided a compound of formula (I) as defined above wherein m represents 0 or 2.

In a further particular aspect of the present invention, there is provided a compound of formula (I) as defined above wherein Z represents CO, $CONR^{10}$ or SO_2.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes single and fused rings wherein at least one ring is aromatic, for example, phenyl, naphthyl, tetrahydronaphthalenyl, indanyl or fluorenyl.

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated ring or a 4-7 membered saturated or partially unsaturated ring fused to a benzene ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, diazepanyl, azepanyl and azocanyl. Suitable examples of benzofused heterocyclic rings include indolinyl, isoindolinyl, benzodioxolyl and dihydroisoquinolinyl.

The term "nitrogen containing heterocyclyl" is intended to represent any heterocyclyl group as defined above which contains a nitrogen atom.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-11 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include furopyridinyl and benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for and are antagonists and/or inverse agonists of the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive dysfunction, epilepsy, neuropathic pain, inflammatory pain, migraine, Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy; psychiatric disorders including schizophrenia, attention deficit hypereactivity disorder, depression and addiction; and other diseases including obesity, asthma,

allergic rhinitis, nasal congestion, chronic obstructive pulmonary disease and gastro-intestinal disorders.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

Preferably, R^1 represents:

hydrogen;

C_{1-6} alkyl (eg. methyl, methylbutyl, or propyl);

C_{1-6} alkoxy (eg. $-OC(CH_3)_3$);

aryl (eg. phenyl, naphthyl, tetrahydronaphthyl, indanyl or fluorenyl);

heteroaryl (eg. benzofuranyl, indolyl, pyrazinyl, benzoxadiazolyl, thiadiazolyl, thienyl, pyrazolopyrimidinyl, pyrazolopyridinyl, benzothiazolyl, furopyridinyl, pyridyl, quinolinyl, isoquinolinyl, quinoxalinyl, cinnolinyl, thiazolyl, triazolyl, isoxazolyl, pyrimidinyl, naphthyridinyl, benzisoxazolyl or benzisothiazolyl);

heterocyclyl (eg. benzodioxolyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrothiopyranyl, thiopyranyl, tetrahydropyranyl, dihydrobenzofuranyl, dihydrochromenyl and xanthenyl);

C_{3-8} cycloalkyl (eg. cyclopropyl, cyclopentyl or cyclohexyl);

$-C_{1-6}$ alkyl-aryl (eg. benzyl);

$-C_{1-6}$ alkyl-C_{3-8} cycloalkyl (eg. $-CH_2$-cyclopropyl);

$-C_{1-6}$ alkyl-heteroaryl (eg. $-CH_2$-pyridyl, $-CH_2$-tetrazolyl, $-CH_2$-triazolyl, $-CH_2$-isothiazolyl, $-CH_2$-thienyl or $-CH_2$-furanyl);

-aryl-heterocyclyl (eg. –phenyl-pyrrolidinyl);

-aryl-aryl (eg. -biphenyl);

-aryl-heteroaryl (eg. –phenyl-pyridyl, -phenyl-pyrrolyl or –phenyl-tetrazolyl); or

-heteroaryl-aryl (eg. –pyridyl-phenyl).

More preferably, R^1 represents unsubstituted phenyl.

Also more preferably, R^1 represents:

aryl (eg. phenyl); or

heterocyclyl (eg. piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or tetrahydropyranyl).

Preferably, R^1 is optionally substituted by one or more (eg. 1, 2 or 3): halogen (eg. chlorine, fluorine or bromine); trifluoromethyl; $-C_{1-6}$ alkyl (eg. methyl, ethyl, isopropyl, propyl or t-butyl) optionally substituted by $COOR^{15}$ (eg. COOH, COOMe or COOEt); $-C_{1-6}$ alkoxy (eg. methoxy, butoxy, $-OCH(Me)_2$ or $-OC(Me)_3$) optionally substituted by $COOR^{15}$ (eg. COOH or COOMe); hydroxy; oxo; cyano; $-C_{1-6}$ alkyl-cyano (eg. $-CH_2$-CN); C_{1-6}

alkenyl (eg. ethenyl) optionally substituted by $COOR^{15}$ (eg. COOMe); C_{3-7} cycloalkyl (eg. cyclopentyl); C_{1-6} alkylsulfonyl (eg. $-SO_2Me$); C_{1-6} alkenoxy (eg. $-OCH_2CH=CH_2$); C_{1-6} alkylthio (eg. –S-ethyl); $NR^{15}R^{16}$ (eg. $N(Me)_2$); $-C_{1-6}$ alkyl-aryl (eg. benzyl); aryl (eg. phenyl); -CO-aryl (eg. –CO-phenyl) optionally substituted by halogen (eg. chlorine); -CO-heteroaryl (eg. –CO-azetidinyl); -CO-heterocyclyl (eg. –CO-tetrahydropyranyl); $-COOR^{15}$ (eg. COOH, COOMe or COOt-butyl); $-COR^{15}$ (eg. –CO-methyl, -CO-ethyl, -CO-isopropyl, -CO-cyclopropyl, -CO-cyclobutyl, -CO-cyclopentyl or -CO-cyclohexyl); $-CONR^{15}R^{16}$ (eg. $-CONH_2$, -CO-pyrrolidinyl, -CO-morpholinyl, -CO-piperazinyl, -CO-piperidinyl, -CO-thiomorpholinyl) optionally substituted by C_{1-6} alkyl (eg. methyl), halogen (eg. fluorine) or $-C_{1-6}$ alkylC_{1-6} alkoxy (eg. $-CH_2$-OMe); or $-C_{1-6}$ alkyl-CO-aryl (eg. $-CH_2$COphenyl) groups.

More preferably, R^1 is optionally substituted by one or more (eg. 1, 2 or 3): halogen (eg. fluorine); oxo; cyano; $-CONR^{15}R^{16}$ (eg. -CO-pyrrolidinyl) or $-COR^{15}$ (eg. -CO-isopropyl, -CO-cyclopropyl or -CO-cyclobutyl).

Preferably, Z represents a bond, CO or $CONR^{10}$. More preferably, Z represents bond or CO, especially CO.
Preferably, R^{10} represents hydrogen or C_{1-6} alkyl.
Preferably, m is 0 or 2, more preferably 0.
Preferably, n is 0 or 1, more preferably n is 0.
When n represents 1, R^2 is preferably halogen (eg. chlorine, bromine or fluorine), trifluoromethyl, cyano or C_{1-6} alkyl (eg. methyl).
Preferably, r is 0.
When r represents 1 or 2, R^2 is preferably C_{1-6} alkyl (eg. methyl) or two R^4 groups together form a bridged CH_2 group.
Preferably, p is 1.
Preferably, R^3 represents $-(CH_2)_q-NR^{11}R^{12}$.
When R^3 represents a group of formula (i), preferably f is 0 or 1, g is 2, h is 1, k is 0 and R^{13} represents hydrogen, optionally substituted C_{1-6} alkyl (eg. ethyl, methylpropyl, isopropyl or methoxyethyl), C_{3-8} cycloalkyl (eg. cyclopropyl, cyclobutyl or cyclopentyl) or $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl (eg. $-CH_2$-cyclopropyl).
When R^3 represents a group of formula (i), more preferably f is 0, g is 2, h is 1, k is 0 and R^{13} represents C_{1-6} alkyl (eg. isopropyl) or C_{3-8} cycloalkyl (eg. cyclopropyl or cyclobutyl).
Preferably, q is 2 or 3, more preferably 3.
Preferably, R^{11} and R^{12} independently represent C_{1-6} alkyl (eg. methyl) or C_{3-8} cycloalkyl (eg. cyclopentyl) or $NR^{11}R^{12}$ represents a heterocyclic group (eg. piperidinyl, pyrrolidinyl, thiomorpholinyl, azepanyl or azocanyl optionally substituted by one or more halogen (eg. fluorine) or C_{1-6} alkyl (eg. methyl or ethyl).
More preferably $NR^{11}R^{12}$ represents pyrrolidinyl, piperidinyl, azepanyl or azocanyl optionally substituted by one or more C_{1-6} alkyl (eg. methyl or ethyl), especially unsubstituted piperidine.

Preferably, -O-R^3 is present at the para position of the phenyl group with respect to the rest of the compound.

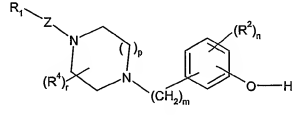
Preferred compounds according to the invention include examples E1-E503 as shown below, or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphuric, citric, lactic, mandelic, tartaric and methanesulphonic. Salts, solvates and hydrates of compounds of formula (I) therefore form an aspect of the invention.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention. For example, when R^3 represents $(CH_2)_qNR^{11}R^{12}$ and $NR^{11}R^{12}$ represents a nitrogen containing heterocyclyl group substituted by one or more C_{1-6} alkyl groups it will be appreciated that the present invention extends to cover diastereomeric and enantiomeric compounds.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

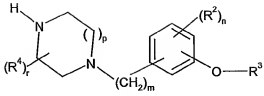
(a) reacting a compound of formula (II)



(II)

wherein R^1, Z, R^4, p, m, r, R^2 and n are as defined above, with a compound of formula $R^{3'}$-L^1, wherein $R^{3'}$ is as defined above for R^3 or a group convertible thereto and L^1 represents a suitable leaving group such as a halogen atom (eg. bromine or chlorine) or an optionally activated hydroxyl group; or

(b) preparing a compound of formula (I) wherein Z represents CO by reacting a compound of formula (III)



(III)

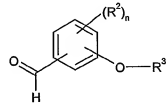
or a protected derivative thereof, wherein R^4, r, p, m, R^2, n and R^3 are as defined above, with a compound of formula R^1-COX, wherein R^1 is as defined above and X represents a suitable leaving group such as an activated hydroxy group, a suitable halogen atom or benzotriazolyl; or

(c) preparing a compound of formula (I) wherein Z represents SO_2 by reacting a compound of formula (III) as defined above with a compound of formula R^1-SO_2Cl, wherein R^1 is as defined above; or

(d) preparing a compound of formula (I) wherein Z represents $NR^{10}CO$ by reacting a compound of formula (III) as defined above with a compound of formula R^1-N=C=O, wherein R^1 is as defined above; or

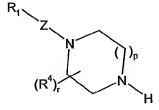
(e) preparing a compound of formula (I) wherein Z represents $CONR^{10}$ by reacting a compound of formula (III) as defined above, sequentially with phosgene in a solvent such as toluene followed by a compound of formula $R^{10}R^1$-NH, in a solvent such as dichloromethane, wherein R^1 and R^{10} are as defined above; or

(f) preparing a compound of formula (I) wherein m represents 1 by reacting a compound of formula (IV)



(IV)

with a compound of formula (XI)



(XI)

or an optionally protected derivative thereof, wherein R^4, r, R^2, n, R^3, R^1, Z and p are as defined above under reducing conditions; or

(g) deprotecting a compound of formula (I) which is protected; and

(h) interconversion to other compounds of formula (I).

When R^3 represents $-(CH_2)_q-NR^{11}R^{12}$, process (a) typically comprises the use of a suitable base, such as potassium carbonate in an appropriate solvent such as 2-butanone optionally in the presence of an activating reagent such as potassium iodide at an appropriate temperature such as reflux.

When a group $R^{3'}$ convertible to R^3 represents, for example, $L^2-(CH_2)_q-$, process (a) typically comprises an alkylation reaction using analogous conditions to those described above.

When R^3 represents a group of formula (i) and L^1 represents an optionally activated hydroxyl group, process (a) typically comprises the use of a phosphine such as triphenylphosphine in a suitable solvent such as tetrahydrofuran, followed by addition of an azodicarboxylate such as diethylazodicarboxylate at a suitable temperature such as room temperature.

Process (b) typically comprises the use of an appropriate solvent such as dichloromethane optionally in the presence of an organic or inorganic base such as potassium carbonate or in the presence of a suitable coupling agent such as 1,3-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole.

Processes (c) and (d) typically comprise the use of a suitable solvent such as 2-butanone.

Process (e) typically comprises the use of a suitable base, such as triethylamine.

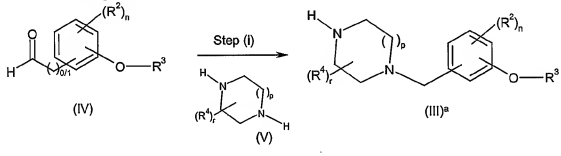
Process (f) comprises the use of reductive conditions (such as treatment with a borohydride eg. sodium triacetoxyborohydride), optionally in the presence of an acid, such as acetic acid, followed by optional deprotection in the event that the compound of formula (XI) is a protected derivative.

In process (g), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-

trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (h) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation. For example, compounds of formula (I) wherein R^3 represents a group of formula (i) may be interconverted at the R^{13} position by reaction with an alkyl halide such as 1-chloro-2-methoxyethane in the presence of a base such as potassium carbonate in a suitable solvent such as 2-butanone optionally in the presence of a transfer reagent such as potassium iodide. Such interconversion may also be carried out by reductive amination, for example, with acetone in the presence of a borohydride such as sodium triacetoxyborohydride and optionally an acid such as acetic acid in a suitable solvent such as dichloromethane.

Compounds of formula (II) and (III) wherein m is 1 or 2 may be prepared in accordance with the following scheme:

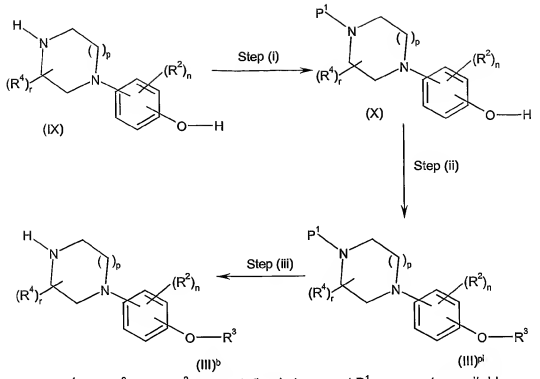


(IV) (V) (III)a

wherein R^4, r, R^2, n, R^3, p are as defined above and the compound of formula (V) may be optionally protected.

Step (i) may be performed in an analogous manner to that described for process (f) above.

Compounds of formula (III) wherein m is 0 may be prepared in accordance with the following scheme:



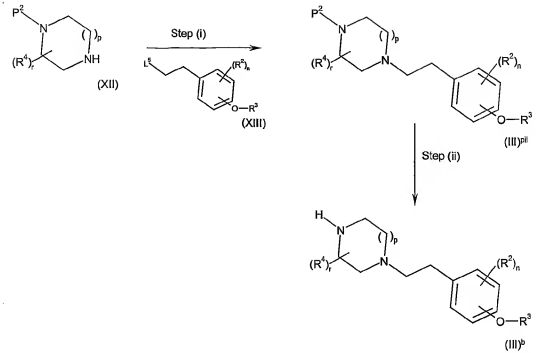
wherein R^4, r, p, R^2, n and R^3 are as defined above and P^1 represents a suitable protecting group (such as Boc).

Step (i) may be performed when P^1 represents Boc by reacting a compound of formula (IX) with di-t-butyl carbonate in the presence of a suitable base (eg. triethylamine) in the presence of a suitable solvent (eg. dichloromethane) at a suitable temperature (eg. room temperature).

Step (ii) may be performed in an analogous manner to the procedures shown below for the preparation of compounds of formula (IV).

Step (iii) typically comprises a deprotection reaction, for example, when P^1 represents Boc, deprotection may typically comprise reaction of a compound of formula $(III)^{pi}$ with hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane.

Compounds of formula (III) wherein m is 2 may be prepared in accordance with the following scheme:

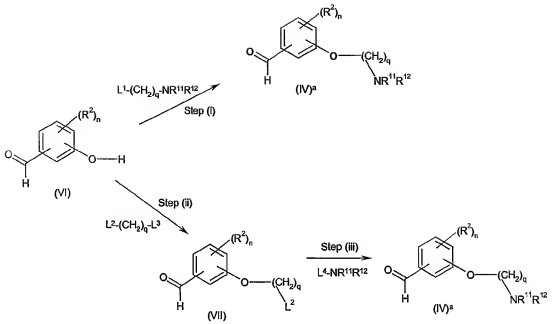


wherein R^2, R^3, R^4, n, p, r are as defined above, P^2 represents a suitable protecting group such as Boc and L^5 represents a suitable leaving group such as a halogen atom (eg. bromine).

Step (i) typically comprises reaction of a compound of formula (XII) with a compound of formula (XIII) in the presence of an inert solvent such as dimethylformamide or acetonitrile.

Step (ii) typically comprises a deprotection reaction, for example, when P^2 represents Boc, deprotection may typically comprise reaction of a compound of formula $(III)^{pII}$ with hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane.

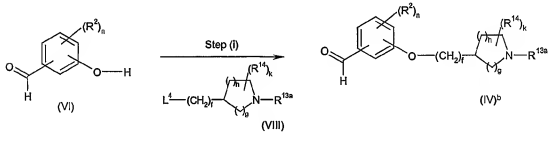
Compounds of formula (IV) wherein R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ may be prepared in accordance with the following scheme:



wherein R^2, n, q, R^{11}, R^{12} are as defined above and L^1, L^2, L^3 and L^4 represent suitable leaving groups (eg. halogen atoms, such as bromine or chlorine).

Steps (i), (ii) and (iii) may be performed using similar conditions to those described for process (a) above.

Compounds of formula (IV) wherein R^3 represents a group of formula (i) as defined above may be prepared in accordance with the following scheme:



wherein R^2, n, f, g, h, k, are as defined above, L^4 represents a suitable leaving group such as a halogen atom or a hydroxyl group and R^{13a} is as defined above for R^{13} or a protecting group such as t-butoxycarbonyl, followed by optional deprotection.

Step (i) may be performed using similar conditions to those described for process (a) above.

Compounds of formula (II) wherein m is 0 may be prepared by a deprotection reaction of a compound of formula (IX) as defined above, followed by an analogous process to

those described in processes (b), (c), (d) and (e) above, optionally followed by hydrolysis treatment to re-generate the free hydroxyl group of formula (II).

Compounds of formula (II) wherein m is 1 or 2 may be prepared from a compound of formula (IV) as defined above in an analogous process to that defined above to prepare compounds of formula (III)[a] followed by an analogous process to those described in processes (b), (c), (d) and (e) above, optionally followed by hydrolysis treatment to re-generate the free hydroxyl group of formula (II).

Compounds of formula (XI) may be prepared from the corresponding piperazine or diazepane by analogous procedures to those described in processes (b), (c), (d) and (e) above.

Compounds of formula (XI) wherein Z represents a bond may be prepared by reacting a compound of formula R^1-L^6 (wherein R^1 is as defined above and L^6 represents a suitable leaving group, eg. a bromine atom) with a compound of formula (XII), such as 1-BOC-piperazine, in the presence of a palladium catalyst, such as tris(dibenzylideneacetone) dipalladium, and a ligand such as 2-cyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl, in an inert solvent such as tetrahydrofuran and in the presence of a base such as lithium bis(trimethylsilyl)amide in an inert atmosphere (nitrogen) and at elevated temperature such as 80°C, according to the procedure of Buchwald, Organic Letters, 2002, 4, 2885-2888.

Compounds of formula (V), (VI), (VIII), (IX), (XII) and (XIII) are either known or may be prepared in accordance with known procedures.

Certain compounds of formula (I), and their pharmaceutically acceptable salts have also been found to have affinity for the histamine H1 receptor.

Histamine H1 receptors are widely distributed throughout the CNS and periphery, and are involved in wakefulness and acute inflammatory processes [Hill et al, Pharmacol. Rev. **49**:253-278 (1997)]. Seasonal allergic rhinitis, and other allergic conditions, are associated with the release of histamine from mast cells. The activation of H1 receptors in blood vessels and nerve endings are responsible for many of the symptoms of allergic rhinitis, which include itching, sneezing, and the production of watery rhinorrhea. Antihistamine compounds, i.e. drugs which are selective H1 receptor antagonists such as chlorphenyramine and cetirizine, are effective in treating the itching, sneezing and rhinorrhea associated with allergic rhinitis, but are not very effective in treating the nasal congestion symptoms [Aaronson, Ann. Allergy, **67**:541-547, (1991)].

H3 receptor agonists are known to inhibit the effect of sympathetic nerve activation on vascular tone in porcine nasal mucosa [Varty & Hey. Eur. J. Pharmacol., **452**:339-345,

(2002)]. In vivo, H3 receptor agonists inhibit the decrease in nasal airway resistance produced by sympathetic nerve activation [Hey et al, Arzneim-Forsch Drug Res., 48:881-888 (1998)]. Furthermore, H3 receptor antagonists in combination with histamine H1 receptor antagonists reverse the effects of mast cell activation on nasal airway resistance and nasal cavity volume, an index of nasal congestion [McLeod et al, Am. J. Rhinol., 13: 391-399, (1999)]. A combined histamine H1 and H3 receptor antagonist, such as the series described herein, would be effective in the treatment of both the nasal congestion and the sneezing, itching and rhinorrhea associated with both seasonal and perennial allergic rhinitis.

Therefore, examples of disease states in which dual histamine H1 and H3 antagonists have potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as asthma (including allergic and non-allergic), allergic rhinitis, sinusitis, bronchitis (including chronic bronchitis), bronchiectasis, chronic obstructive pulmonary disease (COPD) and cystic fibrosis.

Other examples of disease states in which dual histamine H1 and H3 antagonists have potentially beneficial effects include diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure.

Dual histamine H1 and H3 antagonists of the present invention may also be of use in the treatment of sleep/wake disorders, arousal/vigilance disorders, migraine, dementia, mild cognitive impairment (pre-dementia), cognitive dysfunction, Alzheimer's disease, epilepsy, narcolepsy, eating disorders, motion sickness, vertigo, attention deficit hyperactivity disorders, learning disorders, memory retention disorders, schizophrenia, depression, manic disorders, bipolar disorders and diabetes.

Diseases of principal interest for a dual histamine H1 and H3 antagonist include asthma, COPD and inflammatory diseases of the upper respiratory tract involving seasonal and perennial allergic rhinitis, non-allergic rhinitis, and the specific symptoms associated with these diseases including nasal congestion, rhinorrhoea, sneezing, cough and itching (pruritis) of eyes, ears, nose and throat. Other diseases of principal interest include cough, chronic urticaria, allergic conjunctivitis, nasal polyposis, sinusitis, psoriasis, eczema and allergic dermatoses (including urticaria, atopic dermatitis, contact dermatitis, drug rashes and insect bites).

Diseases of principal interest include asthma, COPD, cognitive disorders and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis.

Preferred diseases of principal interest include asthma, cognitive disorders and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis.
Further diseases also of principal interest include inflammatory diseases of the gastrointestinal tract such as inflammatory bowel disease.

Thus the invention also provides a dual histamine H1 and H3 antagonist compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular allergic rhinitis.

Preferred dual histamine H1 and H3 antagonist compounds of formula (I) are those wherein:
R^1 represents aryl (eg. phenyl, naphthyl or tetrahydronaphthyl) or heteroaryl (eg. benzofuranyl, indolyl or quinolinyl);
R^1 is optionally substituted by one or more (eg. 1, 2 or 3): halogen (eg. chlorine, fluorine or bromine); trifluoromethyl; $-C_{1-6}$ alkyl (eg. methyl, ethyl, isopropyl, propyl or t-butyl) optionally substituted by $COOR^{15}$ (eg. COOEt); $-C_{1-6}$ alkoxy (eg. methoxy) optionally substituted by $COOR^{15}$ (eg. COOMe); C_{1-6} alkenyl (eg. ethenyl); $NR^{15}R^{16}$ (eg. $N(Me)_2$); or C_{1-6} alkylthio (eg. –S-ethyl) groups;
Z is a bond or CO;
m is 0 or 2;
n is 0;
r is 0;
p is 1.
R^3 represents $-(CH_2)_q-NR^{11}R^{12}$;
q represents 3; and
$NR^{11}R^{12}$ represents pyrrolidinyl, piperidinyl, azepanyl or azocanyl optionally substituted by one or more C_{1-6} alkyl (eg. methyl or ethyl), more preferably piperidinyl substituted by one or two methyl or ethyl groups.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents (such as corticosteroids (e.g. fluticasone propionate, beclomethasone diproplonate, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (eg. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, lipoxygenase inhibitors, chemokine antagonists (e.g CCR3, CCR1, CCR2, CXCR1, CXCR2), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists)) or beta adrenergic agents (such as salmeterol, salbutamol, formoterol, fenoterol or terbutaline and salts thereof), or sympathomimetics (e.g pseudoephedrine or oxymetazoline), or other antagonists at the histamine receptor (e.g H4), or cholinesterase inhibitors, or cholinergic antagonists, or antiinfective agents (eg. antibiotics, antivirals).

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, topical, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents,

non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-piperazine-1-carboxylic acid tert -butyl ester (D1)

To a solution of 4-(3-(piperidin-1-yl)propoxy)benzaldehyde (WO 02/12214 A2) (1.90g, 7.68mmol) in dichloromethane (25ml) was added 1-N *tert* butoxy carbonyl piperazine (1.57g, 8.45mmol) followed by acetic acid (1ml), and the reaction stirred for 1 hour at room temperature, then treated with sodium triacetoxy borohydride (2g, 9.61mmol) and stirred for 16 hours at room temperature. The reaction was then diluted with saturated sodium bicarbonate solution and extracted with dichloromethane. The dichloromethane was then washed sequentially with water and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield a residue which was purified using silica gel chromatography eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (0.5:4.5:95) to afford the title compound (1.586g, 50%); MS (ES+), m/e 418 $[M+H]^+$.

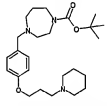
Description 2

1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-piperazine trihydrochloride (D2)

To a solution of 4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester (D1) (1.576g, 3.76mmol) in a (1:1) mixture of dichloromethane and methanol (20ml) was added a 1M solution of hydrogen chloride in diethyl ether (20ml) and the reaction stirred for 5 hours at room temperature. The solvent was then evaporated *in vacuo* and the resulting residue triturated with diethyl ether to afford the title compound (1.5g, 93%); MS (ES+), m/e 318 $[M+H]^+$.

Description 3

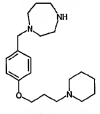
4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane-1-carboxylic acid *tert*-butyl ester (D3)



The title compound (D3) was prepared from [1,4]diazepane-1-carboxylic acid *tert*-butyl ester using the method of Description 1 (D1).
MS(ES+) m/e 432 $[M+H]^+$.

Description 4

1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (D4)



4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane-1-carboxylic acid *tert*-butyl ester (D3) (2.27g, 5.27mmol) was dissolved in dichloromethane (10ml), treated with trifluoroacetic acid (5ml) and stirred at room temperature under argon for 2 hours. The solvent was removed *in vacuo* and the residue dissolved in methanol and passed down an SCX column (10g) eluting with methanol followed by 0.88 ammonia/methanol (1:9). The basic fractions were combined and concentrated *in vacuo* to afford the title compound (1.57g).
MS(ES+) m/e 332 $[M+H]^+$.

Description 5

4-(4-Formyl-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (D5)

4-Hydroxybenzaldehyde (2.0g, 16.4mmol) was dissolved in tetrahydrofuran (20ml) and treated with 4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (4.1g, 20.5mmol) and

triphenylphosphine (5.4g, 20.5mmol). The mixture was cooled in an Ice bath, treated with diethyl azodicarboxylate (3.2ml, 20.5mmol) and allowed to stir at room temperature for 36 hours. The reaction mixture was diluted with ethyl acetate, washed with sodium hydroxide solution (2M), sodium bicarbonate solution and brine. The organic layer was dried under magnesium sulphate, filtered and the solvent removed *in vacuo*. The title compound (1.85g) was obtained by column chromatography eluting with ethyl acetate/hexane (1:4).

^{1}H NMR (CDCl3) δ 9.88 (1H, s), 7.85-7.82 (2H, d), 7.02-6.99 (2H, d), 4.65-4.59 (1H, m), 3.74-3.65 (2H, m), 3.43-3.33 (2H, m), 2.04-1.92 (2H, m), 1.82-1.77 (2H, m), 1.47 (9H, s).

Description 6

4-(4-Piperazin-1-ylmethyl-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (D6)

The title compound (D6) was prepared from 4-(4-formyl-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (D5) and piperazine using the method described in Description 1 (D1). MS(ES+) m/e 376 $[M+H]^+$.

Description 7

4-{4-[4-(1-Phenyl-methanoyl)-piperazin-1-ylmethyl]-phenoxy}-piperidine-1-carboxylic acid tert-butyl ester (D7)

The title compound (D7) was prepared from 4-(4-piperazin-1-ylmethyl-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (D6) and benzoyl chloride using the method described in Example 24 (E24). MS(ES+) m/e 480 $[M+H]^+$.

Description 8

4-(4-Hydroxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (D8)

Di-*tert*-butyl dicarbonate (10.1 g; 1.1 eq) was added portion wise to 4-piperazin-1-yl-phenol (Chem. Pharm. Bull. 49(10), 1314 (2001)) (7.5 g; 42.1 mM) and triethylamine (6.4 ml; 1.1 eq) in dichloromethane (150 ml). The resulting mixture was stirred at room temperature for 18 hours

The reaction was washed with water (2x100 ml), dried (sodium sulphate) and the solvent removed by evaporation *in vacuo*. The residue was purified by column chromatography on silica eluting with 4-1 hexane-ethyl acetate to afford the title compound as an off-white solid (4.71 g)

MS (ES+) m/e 279 $[M+H]^+$.

Description 9

4-[4-(3-Chloro-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D9)

A mixture of 4-(4-hydroxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (D8) (4.0 g; 14.4 mM), 1-bromo-3-chloro propane (1.70 ml; 1.2 eq) and potassium carbonate (4.0 g; 2 eq) in butan-2-one (100 ml) was heated at reflux for 18 hours. The mixture was allowed to cool to room temperature, filtered and evaporated. The residue was purified

by column chromatography on silica eluting with 4-1 hexane – ethyl acetate to afford the title compound as a colourless viscous oil (3.8 g)
MS (ES+) m/e 355 $[M+H]^+$.

Description 10
4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D10)
A mixture of 4-[4-(3-chloro-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D9) (4.0 g; 11.3 mM), piperidine (2.23 ml; 2 eq), potassium carbonate (3.73 g; 2.4 eq) and potassium iodide (3.74 g; 2 eq) in butan-2-one (100 ml) was heated at reflux for 3 days. The mixture was allowed to cool to room temperature, filtered and evaporated to give the title compound as a pale yellow solid (4.6 g)
MS (ES+) m/e 404 $[M+H]^+$.

Description 11
1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine (D11)
A solution of 4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D10) (1.0 g; 2.48 mM) in trifluoroacetic acid (5 ml) was stirred at room temperature for 60 minutes. The resulting mixture was purified on an SCX ion exchange cartridge to afford the title compound as a colourless crystalline solid (0.76 g)
MS (ES+) m/e 304 $[M+H]^+$.

Description 12
4-(3-Hydroxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (D12)
Prepared from 3-piperazin-1-yl-phenol (Chem. Pharm. Bull. 49(10), 1314 (2001)) using the same method described in Description 8 (D8).
MS (ES+) m/e 279 $[M+H]^+$.

Description 13
4-[3-(3-Chloro-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D13)
Prepared from 4-(3-hydroxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (D12) using the same method described in Description 9 (D9).
MS (ES+) m/e 355 $[M+H]^+$.

Description 14
4-[3-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D14)
Prepared from 4-[3-(3-chloro-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D13) using the same method described in Description 10 (D10).
MS (ES+) m/e 404 $[M+H]^+$.

Description 15

1-[3-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine (D15)

Prepared from 4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D14) using the same method described in Description 11 (D11).
MS (ES+) m/e 304 $[M+H]^+$.

Description 16

4-Bromo-1-methyl-1*H*-indole (D16)

A solution of 4-bromo-1*H*-indole (6.7 g) in tetrahydrofuran (75 ml) was treated with sodium hydride (1.24 g) and stirred for 0.5 h at room temperature. The resulting suspension was treated with a solution of iodomethane (2.34 ml) in tetrahydrofuran (35 ml) at 0°C and allowed to warm to room temperature over 1h, whilst stirring. The reaction mixture was poured onto water and partitioned between dichloromethane and water. The organic phase was dried over ($MgSO_4$) and concentrated *in vacuo* to afford *the title compound* (7.2 g). TLC Silica (cyclohexane-ethyl acetate [1:1]), Rf = 0.55.

Description 17

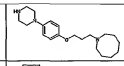
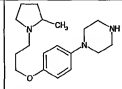
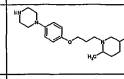
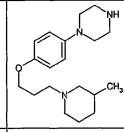
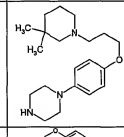
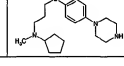
4-Bromo-1-methyl-1*H*-indole-3-carboxylic acid (D17)

A solution of 4-bromo-1-methyl-1*H*-indole (D16) (7.0 g) in tetrahydrofuran (50 ml) was treated with a solution of trifluoroacetic anhydride (5.65 ml) in tetrahydrofuran (20 ml) at 0°C. The reaction mixture was allowed to warm to room temperature over 6 h, whilst stirring. The reaction mixture was concentrated *in vacuo* and then re-suspended in ethanol (25 ml). The solution was treated with 5N sodium hydroxide solution (50 ml) and heated under reflux for 18 h. The reaction mixture was washed with diethyl ether and the aqueous phase acidified with 5N hydrochloric acid solution. The precipitate was filtered, washed with water and concentrated *in vacuo* to afford *the title compound* (4.88 g). TLC, Silica (cyclohexane-ethyl acetate-acetic acid [3:1:0.1]), Rf = 0.35.

Descriptions 18-23

Descriptions 18-23 were prepared using analogous methods to Example 76b by substituting 2-methylpiperidine with the appropriate amine.

Description	Structure	RT (min)	Mass Ion $(M+H)^+$

18		1.64	332
19		0.65	304
20		1.77	346
21		1.45	318
22		1.57	332
23		1.61	318

Descriptions 24-32

Descriptions 24-32 were prepared by analogous methods to those indicated in the below table:

Description	Name	Prepared analogously to	RT (min)
24	1,1-Dimethylethyl 4-(2-naphthalenyl)-1-piperazinecarboxylate	E229a from known starting materials	3.74
25	1,1-Dimethylethyl 4-(4-quinolinyl)-1-piperazinecarboxylate and 1,1-dimethylethyl 4-(3-quinolinyl)-1-piperazinecarboxylate (1:1)	E229a from known starting materials	2.18 & 3.02

26	1-(2-Naphthalenyl)piperazine	E229b from known starting materials	2.00
27	4-(1-Piperazinyl)quinoline and 3-(1-piperazinyl)quinoline (1:1)	E229b from D25	1.18
28	3-{[4-(2-Naphthalenyl)-1-piperazinyl]methyl}phenol	E229c from D24	2.39
29	3-{[4-(1-Naphthalenyl)-1-piperazinyl]methyl}phenol	E229c from D26	2.41
30	4-{[4-(8-Quinolinyl)-1-piperazinyl]methyl}phenol	E229c from E229b	1.78
31	4-{[4-(4-Quinolinyl)-1-piperazinyl]methyl}phenol and 3-{[4-(3-quinolinyl)-1-piperazinyl]methyl}phenol (1:1)	E229c from D27	1.91
32	4-{[4-(1-Naphthalenyl)-1-piperazinyl]methyl}phenol	E229c from D26	2.46

Descriptions 33-42

Descriptions 33-42 were prepared by analogous methods to those indicated in the below table:

Description	Name	Prepared analogously to	RT (min)
33	2-Methyl-4-[4-(2-{4-[(phenylmethyl)oxy]phenyl}ethyl)-1-piperazinyl]quinoline	E237a from known starting materials	2.20
34	2-Methyl-4-[4-(2-{3-[(phenylmethyl)oxy]phenyl}ethyl)-1-piperazinyl]quinoline	E237a from known starting materials	2.11
35	1-(1-Naphthalenyl)-4-(2-{4-[(phenylmethyl)oxy]phenyl}ethyl) piperazine	E237a from known starting materials	2.91
36	1-(1-Naphthalenyl)-4-(2-{3-[(phenylmethyl)oxy]phenyl}ethyl) piperazine	E237a from known starting materials	2.82

37	1-Phenyl-4-(2-{4-[(phenylmethyl)oxy]phenyl}ethyl) piperazine	E237a from known starting materials	2.55
38	4-{2-[4-(2-Methyl-4-quinolinyl)-1-piperazinyl]ethyl}phenol	E237b from D33	1.69
39	3-{2-[4-(2-Methyl-4-quinolinyl)-1-piperazinyl]ethyl}phenol	E237b from D34	4.56
40	4-{2-[4-(1-Naphthalenyl)-1-piperazinyl]ethyl}phenol	E237b from D35	2.28
41	3-{2-[4-(1-Naphthalenyl)-1-piperazinyl]ethyl}phenol	E237b from D36	2.32
42	4-[2-(4-Phenyl-1-piperazinyl)ethyl]phenol	E237b from D37	2.02

Description 43
3-Bromo-4-ethyl-benzoic acid (D43)

To a mixture of conc. HNO_3 (66 mL), glacial AcOH (300 mL) and water (50 mL), 4-ethyl-benzoic acid (15 g) was added, stirring vigorously, before treating with bromine (5.67 mL). Finally a solution of $AgNO_3$ (16.97 g) in water (50 mL) was added dropwise and the mixture was stirred vigorously for 2 h. The precipitate was collected by filtration, washed well with water, before being extracted with hot, saturated K_2CO_3 solution, and then treated with charcoal. The hot solution was filtered through kieselguhr and the solution was acidified to pH1 using conc. HCl. The resulting white precipitate was collected by filtration and dried in the vacuum oven overnight at 60 °C to afford *the title compound* (19.46 g).

NMR ($CDCl_3$) δ 1.26 (3H, t), 2.83 (2H, q), 7.34 (1H, d), 7.97 (1H, dd), 8.27 (1H, dd)

Description 44
Methyl 3-bromo-4-ethyl-benzoate (D44)

3-Bromo-4-ethyl-benzoic acid (D43) (19.40 g) was dissolved in MeOH (200 mL) and then treated with conc. H_2SO_4 (1 mL). The mixture was heated at reflux overnight, and then concentrated under reduced pressure. The residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution, extracting again with EtOAc. The combined

extracts were then washed with brine, dried ($MgSO_4$). The solvent was evaporated *in vacuo* to afford *the title compound* (15.8 g). ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t), 2.79 (2H, q), 3.91 (3H, s), 7.29 (1H, d), 7.89 (1H, dd), 8.19 (1H, d).

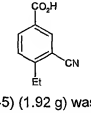
Description 45

Methyl 3-cyano-4-ethyl-benzoate (D45)

Methyl 3-bromo-4-ethyl-benzoate (D44) (5 g) in NMP (180 mL) was treated with copper (I) cyanide (3.69 g). The mixture was then heated at reflux for 5 h, under argon. After cooling to 20 °C the reaction mixture was diluted with water, then filtered through kieselguhr, washing well with water and EtOAc. The organic layer was washed with water, brine and dried over $MgSO_4$. The solvent was evaporated to dryness *in vacuo* and the residue was purified by chromatography on silica eluting with EtOAc- Hexane (1:9) to give *the title compound* (1.9 g) ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, t), 2.94 (2H, q), 3.94 (3H, s), 7.43 (1H, d), 8.17 (1H, dd), 8.28 (1H, d).

Description 46

3-Cyano-4-ethyl benzoic acid (D46)



Methyl 3-cyano-4-ethyl-benzoate (D45) (1.92 g) was dissolved in MeOH (50 mL) before adding 1M NaOH solution (15.24 mL) and stirring the resulting mixture overnight at room temperature, under argon. The reaction mixture was diluted with water, and extracted with EtOAc. The aqueous layer was acidified to pH1 using 2M HCl before extracting with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$ and the solvent evaporated to dryness *in vacuo* to afford *the title compound* (1.63 g). ^{1}H NMR ($CDCl_3$) δ 1.35 (3H, t), 2.97 (2H, q), 7.49 (1H, d), 8.24 (1H, dd), 8.36 (1H, d).

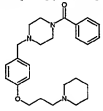
Analysis of the Examples was performed as follows:

LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% formic acid and 0.01M ammonium acetate in water (solvent A) and 0.05% formic acid and 5% water in acetonitrile (solvent B), using the following elution gradient 0.0-7min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5min 0%B at a flow rate of 3 mL/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

Preparative mass directed HPLC was conducted on a Waters FractionLynx system comprising of a Waters 600 pump with extended pump heads, Waters 2700 autosampler, Waters 996 diode array and Gilson 202 fraction collector on a 10 cm X 2.54 cm ID ABZ+ column, eluting with 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B), using an appropriate elution gradient, at a flow rate of 20 ml/min and detecting at 200-320 nm at room temperature. Mass spectra were recorded on Micromass ZMD mass spectrometer using electrospray positive and negative mode, alternate scans. The software used was *MassLynx 3.5* with *OpenLynx* and *FractionLynx* options.

Example 1

1-Phenyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E1)



N-Cyclohexylcarbodiimide, N-methyl polystyrene HL (200-400 mesh) 1.8mMol/g (650mg, 1.172mmol) was suspended in a (1:1) mixture of dichloromethane and dimethylformamide and treated sequentially with benzoic acid (72mg, 0.58mmol), 1-hydroxybenzotriazole hydrate (80mg, 0.58mmol) and stirred for 10 minutes at room temperature. A solution of 1-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazine trihydrochloride (D2) (125mg, 0.29mmol) in dichloromethane (1ml) and triethylamine (0.13ml, 0.87mmol) was then added to the reaction and stirred at room temperature for 16 hours. After filtration, the filtrate was applied to a Mega Bond elute SCX ion exchange column washing sequentially with water and methanol, followed by 0.880 ammonia/methanol (1:10) to elute the crude reaction mixture. Purification by silica gel chromatography eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (0.5:4.5:95) to afford the title product (95mg, 77%); MS (ES+), m/e 422 $[M+H]^+$.

Examples 2-11

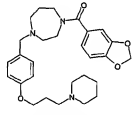
Examples 2-11 (E2-E11) were prepared from Description 2 (D2) using an analogous method to that described in Example 1 (E1) by substituting benzoic acid for the appropriate acid indicated in the table.

Example	Acid	Mass Spectrum
1-Benzo[1,3]dioxol-5-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E2)	piperonylic acid	MS (ES+) m/e 466 $[M+H]^+$
1-Naphthalen-2-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-	2-naphthoic acid	MS (ES+) m/e 472 $[M+H]^+$

methanone (E3)		
1-(3,5-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E4)	3,5-dichlorobenzoic acid	MS (ES+) m/e 491/493 $[M+H]^+$
1-(4-Bromo-3-methyl-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E5)	3-methyl, 4-bromo benzoic acid	MS (ES+) m/e 515/517 $[M+H]^+$
1-(2-Methoxy-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E6)	2-methoxy benzoic acid	MS (ES+) m/e 452 $[M+H]^+$
1-(3,4-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E7)	3,4-dichloro benzoic acid	MS (ES+) m/e 491/493/495 $[M+H]^+$
4-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanoyl)-benzonitrile (E8)	4-cyano benzoic acid	MS (ES+) m/e 447 $[M+H]^+$
1-(4-Fluoro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E9)	4-fluoro benzoic acid	MS (ES+) m/e 440 $[M+H]^+$
1-(4-Bromo-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E10)	4-bromo benzoic acid	MS (ES+) m/e 500/502 $[M+H]^+$
1-Benzofuran-2-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E11)	2-benzofuran carboxylic acid	MS (ES+) m/e 462 $[M+H]^+$

Example 12

1-Benzo[1,3]dioxol-5-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E12)



1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (D4) (100mg, 0.30mmol) was dissolved in dichloromethane (5ml) and treated sequentially with benzo[1,3]dioxole-5-carboxylic acid (125mg, 0.75mmol), 1,3-dicyclohexylcarbodiimide (155mg, 0.75mmol) and 1-hydroxybenzotriazole hydrate (101mg, 0.75mmol). The mixture was allowed to stir at room temperature under argon for 12 hours, diluted with methanol and passed down an SCX ion exchange column (2g) eluting with methanol followed by 0.880

ammonia/methanol (1:9). The basic fractions were combined and concentrated *in vacuo* to afford the title compound (127mg). MS(ES+) *m/e* 480 $[M+H]^+$.

Examples 13-15

Examples 13-15 (E13-E15) were prepared from Description 4 (D4) using an analogous method to that described in Example 12 (E12) by substituting benzo[1,3]dioxole-5-carboxylic acid for the appropriate acid indicated in the table.

Example	Carboxylic acid	Mass Spectrum
1-Phenyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E13)	Benzoic acid	MS(ES+) m/e 436 $[M+H]^+$
1-Naphthalen-2-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E14)	Naphthalene-2-carboxylic acid	MS(ES+) m/e 486 $[M+H]^+$
1-(3,5-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E15)	3,5-Dichloro-benzoic acid	MS(ES+) m/e 505 $[M+H]^+$

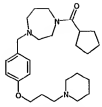
Examples 16-23

Examples 16-23 (E16-E23) were prepared from Description 4 (D4) using an analogous method to that described in Example 12 (E12) by substituting benzo[1,3]dioxole-5-carboxylic acid for the appropriate acid indicated in the table followed by further purification by column chromatography on silica gel eluting with a mixture of .880 ammonia/methanol/dichloromethane (0.5:4.5:95).

Example	Carboxylic acid	Mass Spectrum
1-(4-Bromo-3-methyl-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E16)	4-Bromo-3-methyl-benzoic acid	MS(ES+) m/e 529 $[M+H]^+$
1-(2-Methoxy-phenyl)-1-{4-[4-(3-piperidin-1-	2-Methoxy-benzoic acid	MS(ES+) m/e 466 $[M+H]^+$

yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E17)		
4-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanoyl)-benzonitrile (E18)	4-Cyano-benzoic acid	MS(ES+) m/e 461 $[M+H]^+$
1-(4-Fluoro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E19)	4-Fluoro-benzoic acid	MS(ES+) m/e 454 $[M+H]^+$
1-(4-Bromo-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E20)	4-Bromo-benzoic acid	MS(ES+) m/e 515 $[M+H]^+$
1-Benzofuran-2-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E21)	Benzofuran-2-carboxylic acid	MS(ES+) m/e 476 $[M+H]^+$
1-(3,4-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E22)	3,4-Dichloro-benzoic acid	MS(ES+) m/e 505 $[M+H]^+$
1-Cyclopropyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E23)	Cyclopropane carboxylic acid	MS(ES+) m/e 400 $[M+H]^+$

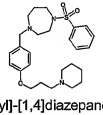
Example 24
1-Cyclopentyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E24)



1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (D4) (100mg, 0.30mmol) was dissolved in dichloromethane (5ml), treated with cyclopentyl acid chloride (80mg, 0.60mmol), potassium carbonate (83mg, 0.60mmol) and allowed to stir at room temperature under argon for 12 hours. The reaction mixture was diluted with methanol and passed down an SCX column (2g) eluting with methanol followed by ammonia/methanol (1:9). The basic fractions were combined and concentrated *in vacuo* to afford the title compound (56mg). MS(ES+) *m/e* 428 $[M+H]^+$.

Example 25

1-Benzenesulfonyl-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E25)



1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (D4) (100mg, 0.30mmol) was dissolved in 2-butanone (5ml), treated with benzene sulfonyl chloride (57mg, 0.32mmol) and allowed to stir at room temperature under argon for 2 hours. The reaction mixture was diluted with methanol and passed down an SCX column (2g) eluting with methanol followed by ammonia/methanol (1:9). The basic fractions were combined and concentrated *in vacuo* to afford the title compound (91mg). MS(ES+) *m/e* 472 $[M+H]^+$.

Examples 26-28

Examples 26-28 (E26-E28) were prepared from Description 4 (D4) using an analogous method to that described in Example 25 (E25) by substituting benzenesulfonyl chloride for the appropriate sulfonyl chloride indicated in the table.

Example	Sulfonyl Chloride	Mass Spectrum
1-(Naphthalene-2-sulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E26)	Naphthalene-2-sulfonyl chloride	MS(ES+) m/e 522 $[M+H]^+$
1-(4-Fluoro-benzenesulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E27)	4-Fluoro-benzenesulfonyl chloride	MS(ES+) m/e 490 $[M+H]^+$
1-(4-Bromo-benzenesulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-	4-Bromo-benzenesulfonyl	MS(ES+) m/e 552 $[M+H]^+$

[1,4]diazepane (E28)	chloride	

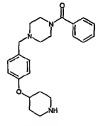
Examples 29-31

Examples 29-31 (E29-E31) were prepared from Description 4 (D4) using an analogous method to that described in Example 25 (E25) by substituting benzenesulfonyl chloride for the appropriate sulfonyl chloride indicated in the table followed by further purification by column chromatography on silica gel eluting with a mixture of .880 ammonia/methanol/dichloromethane (0.5:4.5:95).

Example	Sulfonyl Chloride	Mass Spectrum
1-(3,5-Dichloro-benzenesulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E29)	3,5-Dichloro-benzenesulfonyl chloride	MS(ES+) m/e 540 $[M+H]^+$
1-(3,4-Dichloro-benzenesulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E30)	3,4-Dichloro-benzenesulfonyl chloride	MS(ES+) m/e 540 $[M+H]^+$
4-{4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane-1-sulfonyl}-benzonitrile (E31)	4-Cyano-benzenesulfonyl chloride	MS(ES+) m/e 497 $[M+H]^+$

Example 32

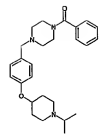
1-Phenyl-1-{4-[4-(piperidin-4-yloxy)-benzyl]-piperazin-1-yl}-methanone (E32)



The title compound (E32) was prepared from 4-[4-[4-(1-phenyl-methanoyl)-piperazin-1-ylmethyl]-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester (D7) using the method described in Description 4 (D4). MS(ES+) m/e 380 $[M+H]^+$.

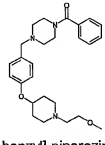
Example 33

1-{4-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperazin-1-yl}-1-phenyl-methanone (E33)



The title compound (E33) was prepared from 1-phenyl-1-{4-[4-(piperidin-4-yloxy)-benzyl]-piperazin-1-yl}-methanone (E32) and acetone using the method described in Description 1 (D1). MS(ES+) m/e 422 $[M+H]^+$.

Example 34
1-(4-{4-[1-(2-Methoxy-ethyl)-piperidin-4-yloxy]-benzyl}-piperazin-1-yl)-1-phenyl-methanone (E34)



1-Phenyl-1-{4-[4-(piperidin-4-yloxy)-benzyl]-piperazin-1-yl}-methanone (E32) (150mg, 0.40mmol) was dissolved in 2-butanone and treated with 1-chloro-2-methoxy-ethane (0.08ml, 0.80mmol), potassium carbonate (132mg, 0.96mmol) and potassium iodide (159mg, 0.96mmol). The reaction mixture was heated under reflux for 24 hours. The mixture was allowed to cool to room temperature, acidified by the addition of glacial acetic acid and passed down an SCX ion exchange column (2g) eluting with methanol followed by ammonia/methanol (1:9). The basic fractions were combined and concentrated *in vacuo* to afford the title compound (76mg). MS(ES+) *m/e* 438 $[M+H]^+$.

Examples 35-37

Examples 35-37 (E35-E37) were prepared in accordance with the following general synthesis:

The appropriate acid chloride (1.1 eq) was added to a mixture of 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (100 mg; 0.33 mM) and potassium carbonate (55 mg; 1.5 eq) in butan-2-one (2 ml). The resulting mixtures were stirred at room temperature for 3 hours and then purified on SCX ion exchange cartridges to afford the title compounds.

Example	Acid Chloride	Mass Spectrum
1-Cyclopropyl-1-{4-[4-(3-piperidin-	Cyclopropane	MS (ES+) m/e 372

1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E35)	carbonyl chloride	$[M+H]^+$.
1-Phenyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E36)	Benzoyl chloride	MS (ES+) m/e 408 $[M+H]^+$.
1-(3,4-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E37)	3,4-Dichlorobenzoyl chloride	MS (ES+) m/e 477 $[M+H]^+$.

Examples 38-39

Examples 38-39 (E38-E39) were prepared from 1-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D15) using the same procedure as described in Examples 36 and 37, respectively.

Example	Mass Spectrum
1-Phenyl-1-{4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E38)	MS (ES+) m/e 408 $[M+H]^+$.
1-(3,4-Dichloro-phenyl)-1-{4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E39)	MS (ES+) m/e 477 $[M+H]^+$.

Examples 40-42

Examples 40-42 (E40-E42) were prepared in accordance with the following general synthesis:

The appropriate sulphonyl chloride (1.1 eq) was added to a mixture of 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (100 mg; 0.33 mM) and potassium carbonate (55 mg; 1.5 eq) in butan-2-one (2 ml). The resulting mixtures were stirred at room temperature for 3 hours and then purified on SCX ion exchange cartridges to afford the title compounds.

Example	Sulfonyl Chloride	Mass Spectrum
1-Methanesulphonyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E40)	Methane sulfonyl chloride	MS (ES+) m/e 382 $[M+H]^+$.
1-Benzenesulphonyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E41)	Benzene sulfonyl chloride	MS (ES+) m/e 444 $[M+H]^+$.
1-(3,4-Dichloro benzenesulphonyl)-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E42)	3,4-Dichlorobenzene sulfonyl chloride	MS (ES+) m/e 513 $[M+H]^+$.

Examples 43-45

Examples 43-45 (E43-E45) were prepared from 1-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D15) using the same procedure as described in Examples 40, 41 and 42, respectively.

Example	Mass Spectrum
1-Methanesulphonyl-4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E43)	MS (ES+) m/e 382 $[M+H]^+$.
1-Benzenesulphonyl-4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E44)	MS (ES+) m/e 444 $[M+H]^+$.
1-(3,4-Dichloro benzenesulphonyl)-4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E45)	MS (ES+) m/e 513 $[M+H]^+$.

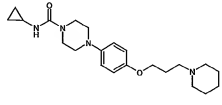
Examples 46-47

Examples 46-47 (E46-E47) were prepared in accordance with the following general synthesis:

The appropriate isocyanate (1.1 eq) was added to 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (100 mg; 0.33 mM) in butan-2-one (2 ml). The resulting mixtures were stirred at room temperature for 3 hours and then purified on SCX ion exchange cartridges to afford the title compounds.

Example	Isocyanate	Mass Spectrum
4-[4-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid phenylamide (E46)	Isocyanatobenzene	MS (ES+) m/e 423 $[M+H]^+$.
4-[4-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide (E47)	3,4-Dichloro isocyanato benzene	MS (ES+) m/e 492 $[M+H]^+$.

Example 48
4-[4-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid cyclopropylamide (E48)



To a solution of 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (150 mg; 0.49 mM) in dry dichloromethane (3 ml) was added drop wise a 20% solution of phosgene in toluene (0.5 ml; ~2 eq) and the resulting mixture stirred for 1 hour. The solvent was

removed by evaporation and the resulting white powder dissolved in dry dichloromethane (4 ml). Triethylamine (0.14 ml: 2 eq) was added followed by cyclopropylamine (0.1 ml; 3 eq) and the mixture stirred for 18 hours. The solvent was removed by evaporation *in vacuo* and the residue purified on a silica column eluting with 3% methanol in dichloromethane to afford the title compound as a white solid (155 mg) MS (ES+) m/e 387 $[M+H]^+$.

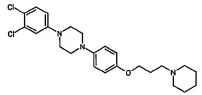
Examples 49-50

Examples 49-50 (E49-E50) were prepared from 1-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D15) using the same procedure as described in Examples 46 and 47, respectively.

Example	Mass Spectrum
4-[3-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid phenylamide (E49)	MS (ES+) m/e 423 $[M+H]^+$.
4-[3-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide (E50)	MS (ES+) m/e 492 $[M+H]^+$.

Example 51

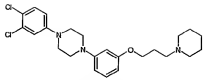
1-(3,4-Dichloro-phenyl)-4-[4-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine (E51)



Tris(dibenzylidineacetone) di palladium (0) (5 mol%; 23 mg) was added to a mixture of 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (150 mg; 0.49 mmol), 3,4-dichloro bromo benzene (160 mg; 1.2 eq), sodium *tert*-butoxide (71 mg; 1.1 eq) and racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (7.5 mol%; 24 mg) in dry toluene (3ml). The resulting mixture was heated at reflux under argon for 18 hours. The reaction was allowed to cool to room temperature and diluted with ethyl acetate (10 ml). The resulting solids were removed by filtration and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography on silica eluting with 3% methanol in dichloromethane to afford the title compound as a buff solid (45 mg)
MS (ES+) m/e 448 $[M+H]^+$.

Example 52

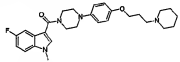
1-(3,4-Dichloro-phenyl)-4-[3-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine (E52)



The title compound (E52) was prepared from 1-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D15) using the same method as described in Example 51 (E51).
MS (ES+) m/e 448 $[M+H]^+$.

Example 53

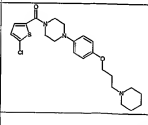
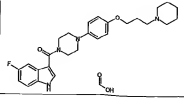
5-Fluoro-1-methyl-3-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}-1*H*-indole (E53)

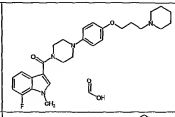
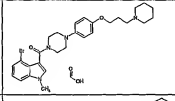
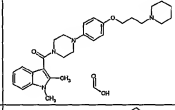
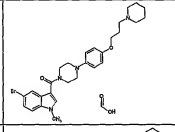
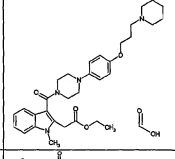
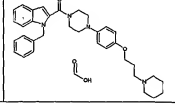


A solution of 5-fluoro-1-methyl-1*H*-indole-3-carboxylic acid [WO 0071537 A1] (35 mg) and 1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (D11) (50 mg) in dichloromethane (1ml) was treated with benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (94.4 mg) and heated in a microwave (CEM™ Discover microwave) at 120°C for 5 min. The reaction mixture was concentrated *in vacuo* and purified on a SCX cartridge (2g) eluting with methanol-aqueous ammonia (10:1) followed by mass directed auto preparative HPLC to give *the title compound* (12 mg). LCMS RT = 2.49 min, 478 $(M+H)^+$

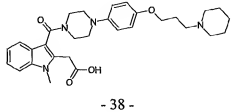
Examples 54-61

The following compounds were prepared in an analogous manner to the process described for E53 from D11 and a known appropriate acid, with the exception of Example 57 which was prepared from D11 and D17.

Example	Structure	RT (min)	Mass Ion $(M+H)^+$
54		2.37	448 450
55		2.26	464

56		2.41	478
57		2.40	539 541
58		2.32	474
59		2.56	539 541
60		2.54	546
61		2.80	536

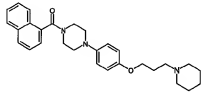
Example 62
(1-Methyl-3-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}-1*H*-indol-2-yl)acetic acid (E62)



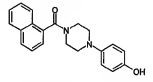
A solution of ethyl (1-methyl-3-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}-1*H*-indol-2-yl)acetate (E60) [54 mg] in methanol [6 ml] and water [0.8 ml] was treated with 2N sodium hydroxide [0.46 ml] and was heated under reflux for 2 h. The reaction mixture was quenched with hydrochloric acid [10 ml] at room temperature. The reaction mixture was concentrated *in vacuo* and partitioned between ethyl acetate and water. The organic phase was dried and concentrated *in vacuo* to give *the title compound* (20 mg). LCMS RT = 2.35 min, 518 $(M+H)^+$

Example 63

1-(1-Naphthoyl)-4-[4-(3-piperidin-1-ylpropoxy)phenyl]piperazine trifluoroacetate (E63)



E63a: 4-[4-(1-Naphthoyl)piperazin-1-yl]phenol



To a stirring mixture of 4-(1-piperazinyl)phenol (5.54 g) and triethylamine (10.83 ml) in dichloromethane (140 ml) was added dropwise, 1-naphthalenecarbonyl chloride (9.83 ml). The resulting reaction mixture was stirred under a nitrogen atmosphere for 3 h. The mixture was partitioned between dichloromethane and water and the organic phase was washed with saturated brine, dried ($MgSO_4$) and evaporated to dryness. The residue was suspended in 6:4 tetrahydrofuran-methanol (370 ml) and treated with a saturated solution of potassium carbonate in methanol (45 ml). The mixture was stirred at room temperature under a nitrogen atmosphere for 20 h. The solvent was evaporated and the residue was partitioned between dichloromethane and water. The organic phase was washed with saturated brine, dried ($MgSO_4$) and evaporated to give an oil (15.5 g), part of which (14.5 g) was purified by chromatography on a silica SPE bond elut cartridge eluting with 10% -80% ethyl acetate - cyclohexane gradient to give *the title compound* (8.9g). LCMS RT = 2.97 min.

E63b: 1-[4-(3-Chloropropoxy)phenyl]-4-(1-naphthoyl)piperazine

Was prepared from 4-[4-(1-naphthoyl)piperazin-1-yl]phenol (E63a) and 1-bromo-3-chloropropane using the same method described in Description 9 LCMS RT = 3.59 min

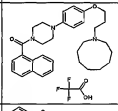
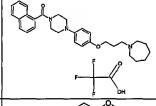
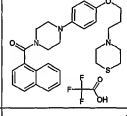
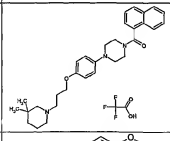
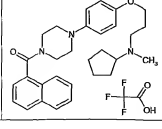
E63c: 1-(1-Naphthoyl)-4-[4-(3-piperidin-1-ylpropoxy)phenyl]piperazine trifluoroacetate

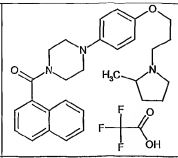
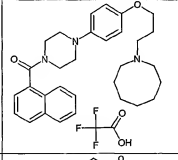
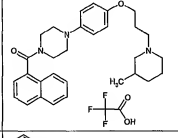
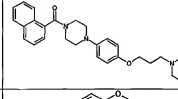
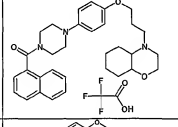
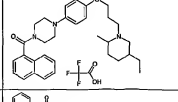
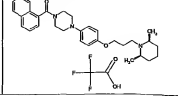
1-[4-(3-Chloropropoxy)phenyl]-4-(1-naphthoyl)piperazine (E63b) (27 mg) piperidine (0.033 ml), potassium carbonate (46 mg), potassium iodide (56 mg)in 2-butanone (2 ml) was heated to reflux for 36 h. The solvent was removed at room temperature by a stream of nitrogen gas. The residue was dissolved in water and dichloromethane. The

organic layer was separated, concentrated and purified by mass directed preparative HPLC to give *the title compound* (23 mg). LCMS RT = 2.15 min, ES+ve m/z 458 $(M+H)^+$.

Examples 64-75

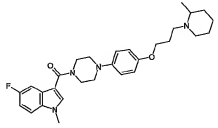
Examples 64-75 were prepared in an array format using the same method described in Example 63c from 1-[4-(3-chloropropoxy)phenyl]-4-(1-naphthoyl)piperazine (0.067 mmol), the appropriate secondary amine (5.0 eq), potassium carbonate (5.0 eq), and potassium iodide (5.0 eq) in 2-butanone (2 ml). The products were purified by mass directed auto-preparative HPLC to provide the compounds as TFA salts.

Example	Structure	RT (min)	Mass Ion $(M+H)^+$
64		2.76	500
65		2.63	472
66		2.55	476
67		2.27	486
68		2.66	472

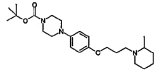
69		2.58	458
70		2.71	485.73
71		2.22	472
72		2.22	472
73		2.26	514
74		2.35	500
75		2.24	486

Example 76

5-Fluoro-1-methyl-3-[(4-{4-[3-(2-methylpiperidin-1-yl)propoxy]phenyl}piperazin-1-yl)carbonyl]-1*H*-indole (E76)

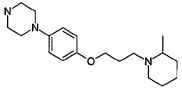


E76a: 1,1-Dimethylethyl 4-(4-{[3-(2-methyl-1-piperidinyl)propyl]oxy}phenyl)-1-piperazinecarboxylate



1,1-Dimethylethyl 4-{4-[(3-chloropropyl)oxy]phenyl}-1-piperazinecarboxylate (D9) (1.6g), was dissolved in 2-butanone (10ml). Potassium carbonate (1.38g) and a catalytic amount of potassium iodide were added, followed by 2-methylpiperidine (0.99g). The mixture was heated at reflux for 72 h under nitrogen. The reaction mixture was diluted with water and extracted with dichloromethane. The organic phases were separated using a hydrophobic frit, combined and evaporated *in vacuo*. The residue was purified on a 100g silica SPE bond elut cartridge, eluting with a gradient of 0% to 20% [0.880 ammonia-methanol (1:9)]-dichloromethane mixtures, to give *the title compound* (1.66g). LCMS RT= 2.48min.

E76b: 1-(4-{[3-(2-Methyl-1-piperidinyl)propyl]oxy}phenyl)piperazine



1,1-Dimethylethyl 4-(4-{[3-(2-methyl-1-piperidinyl) propyl]oxy}phenyl)-1-piperazinecarboxylate (E76a) (1.66 g) was dissolved in dry dichloromethane (25 ml) and stirred under nitrogen. 50% Trifluoroacetic acid in dichloromethane (5ml) was added, and the mixture was stirred at room temperature for 4 h. Saturated sodium bicarbonate solution was then added and the mixture was extracted with dichloromethane. The organic phase was separated using a hydrophobic frit, and evaporated *in vacuo*, however, most of the product was in the aqueous phase. The product was removed from the aqueous phase using an OASIS cartridge, washing with water and eluting with methanol, and further purified using an aminopropyl bond elut cartridge, eluting with dichloromethane and then SCX cartridge, eluting with 50% [0.880 ammonia-methanol

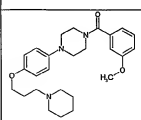
(1:9)]-dichloromethane to give *the title compound* (0.94 g). LCMS RT= 1.01min, ES+ve m/z = 318 $(M+H)^+$

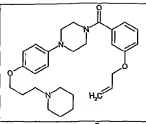
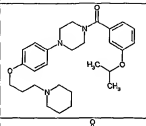
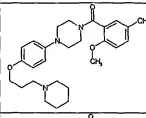
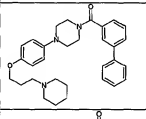
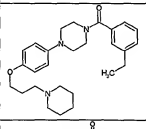
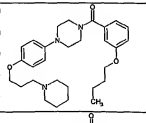
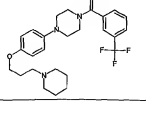
E76c: 5-Fluoro-1-methyl-3-[(4-[4-[3-(2-methylpiperidin-1-yl)propoxy]phenyl}piperazin-1-yl)carbonyl]-1*H*-indole

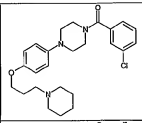
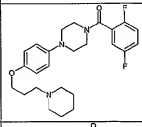
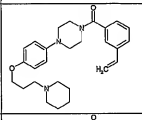
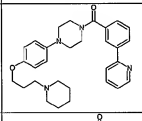
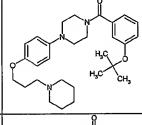
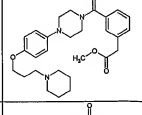
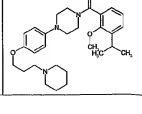
A solution of 5-fluoro-1-methyl-1*H*-indole-3-carboxylic acid (19.3 mg) and *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU) (56mg) in DMF (1 ml) and diisopropylethylamine (0.035 ml) was stirred for 10 min before 1-{4-[3-(2-methylpiperidin-1-yl)propoxy]phenyl}piperazine (E76b) (21.3 mg) in DMF (0.5 ml) was added. The mixture was stirred for 18 h and then concentrated under reduced pressure. The residue was purified by SPE ion exchange chromatography on an SCX-2 cartridge (1g). The cartridge was washed with methanol (3 ml) and the product eluted with 2M ammonia in methanol (2.5 ml), to give *the title compound* (15 mg) LCMS RT = 2.42 min, ES+ve m/z 493 $(M+H)^+$.

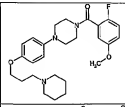
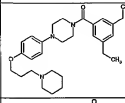
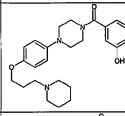
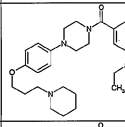
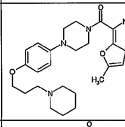
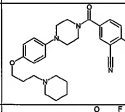
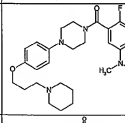
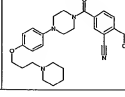
Examples 77-224

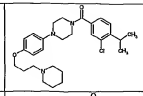
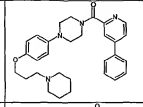
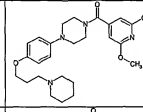
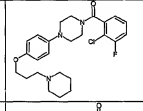
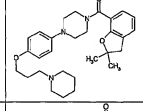
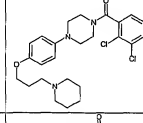
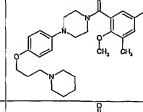
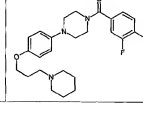
Examples 77 to 224 were prepared in an array format in vials using a solution of the appropriate carboxylic acid (0.1 mmol) in DMF (0.5 ml) and a solution of *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU) (0.15mmol) in DMF (0.5 ml) and diisopropylethylamine (0.2 mmol). Each vial was shaken manually and stood for 10 min, before a solution of the appropriate piperazine (selected from D18-D23 or D46 in the case of Example 99) (0.067 mmol) in DMF (0.5 ml) was added to each reaction mixture. The vials were left to stand overnight for approximately 18 h at room temperature. Each solution was then added to the top of a preconditioned SCX-2 SPE cartridge (1g). The cartridge was washed with methanol (3 ml) and the product eluted with 2M ammonia in methanol (2.5 ml), into pre-weighed vials. The solutions were evaporated to dryness on the genevac to provide the products (Examples 77-222). Examples 151, 154, 162-171 and 206-222 were further purified by mass directed auto-preparative HPLC to provide the products as trifluoroacetate salts.

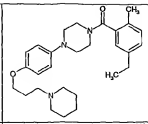
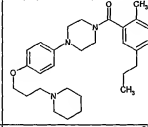
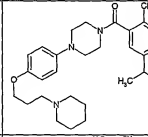
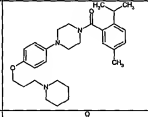
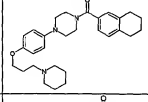
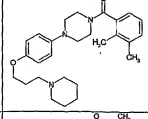
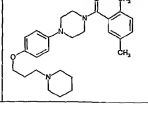
Example	Structure	RT (min)	Mass ion $(M+H)^+$
77		2.36	438

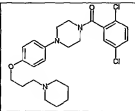
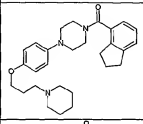
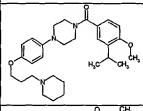
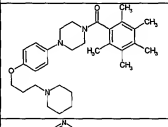
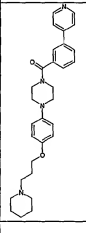
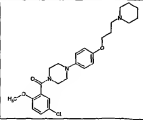
78		2.52	464
79		2.55	466
80		2.44	452
81		2.74	484
82		2.52	436
83		2.74	480
84		2.58	476

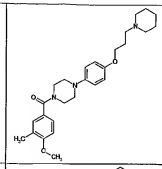
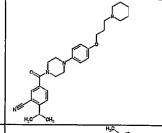
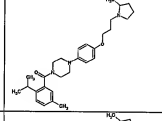
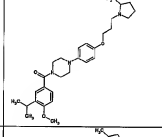
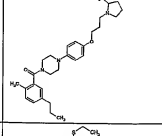
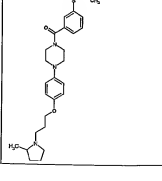
85		2.50	442 444
86		2.39	444
87		2.50	434
88		2.36	485
89		2.58	480
90		2.34	480
91		2.66	480

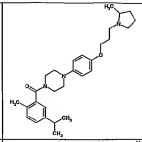
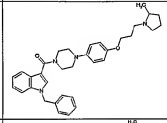
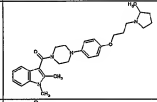
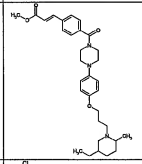
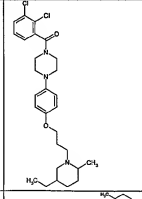
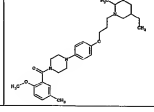
92		2.23	456
93		2.76	464
94		2.24	424
95		2.16	468
96		1.87	463
97		1.96	463
98		1.85	467
99		2.11	461

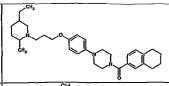
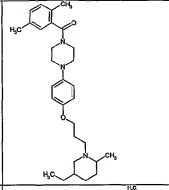
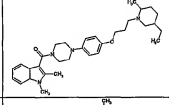
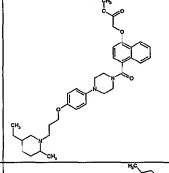
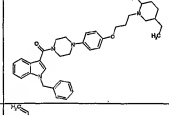
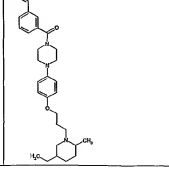
100		2.37	484
101		2.11	485
102		2.05	473 475
103		2.07	460 462
104		2.07	478
105		2.18	476 478
106		2.13	466
107		2.05	440

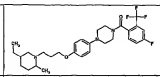
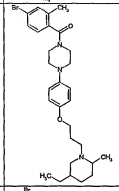
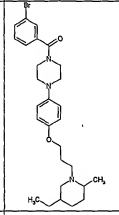
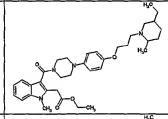
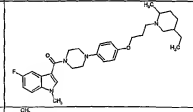
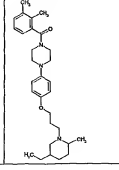
108		2.20	450
109		2.31	464
110		2.31	464
111		2.29	464
112		2.22	462
113		2.07	436
114		2.07	436

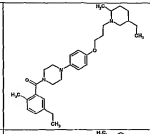
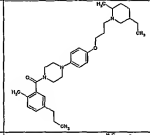
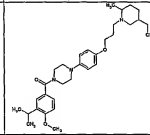
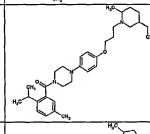
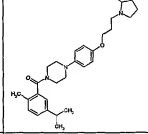
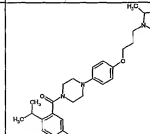
115		2.12	476 478
116		2.13	448
117		2.26	480
118		2.29	478
119		2.15	485
120		2.52	472

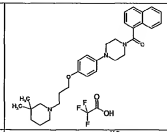
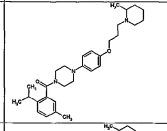
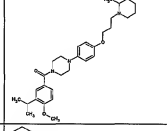
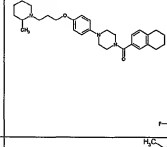
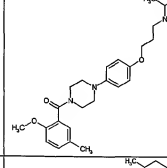
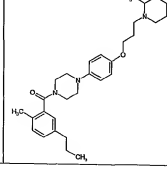
121		2.52	452
122		2.63	475
123		2.53	464
124		2.53	480
125		2.60	464
126		2.47	468

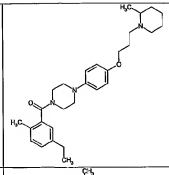
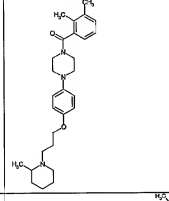
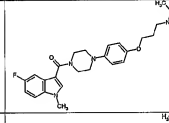
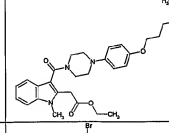
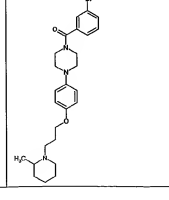
127		2.59	464
128		2.61	537
129		2.37	475
130		2.58	534
131		2.66	518 520
132		2.54	494

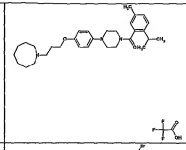
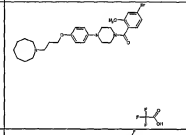
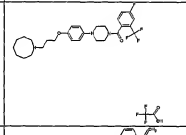
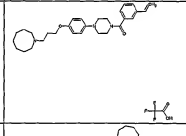
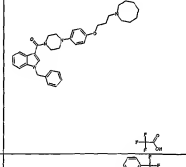
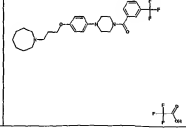
133		2.76	504
134		2.60	478
135		2.60	517
136		2.65	588
137		2.83	579
138		2.60	476

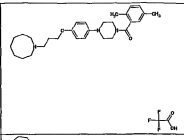
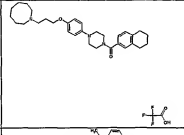
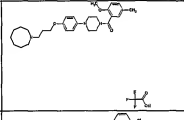
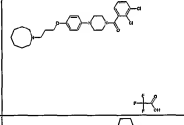
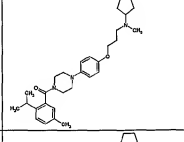
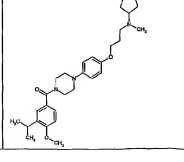
139		2.63	536
140		2.69	542 544
141		2.62	528 530
142		2.68	589
143		2.61	521
144		2.58	478

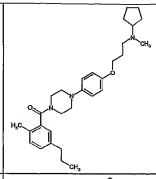
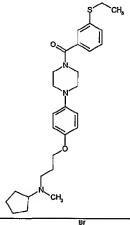
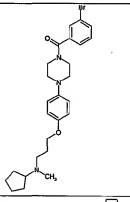
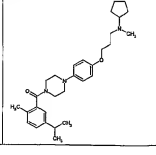
145		2.70	492
146		2.81	506
147		2.77	522
148		2.77	506
149		2.59	464
150		2.57	464

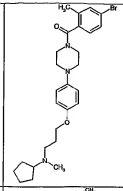
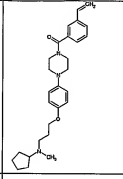
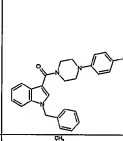
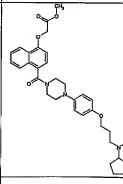
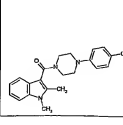
151		2.27	486
152		2.60	478
153		2.63	494
154		2.36	466
155		2.36	466
156		2.65	478

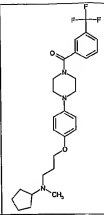
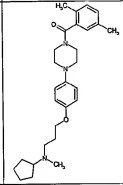
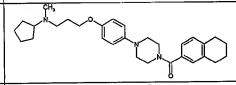
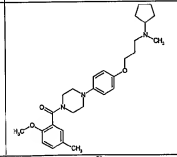
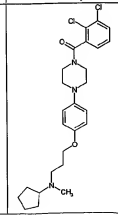
157		2.54	464
158		2.40	450
159		2.42	493
160		2.42	561
161		2.51	500 502

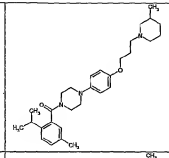
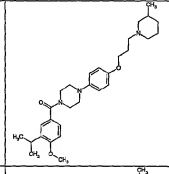
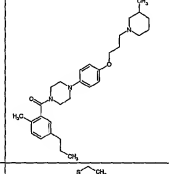
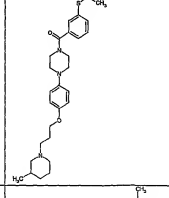
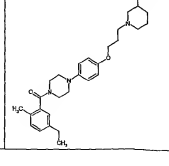
162		2.66	492
163		2.60	528 530
164		2.54	522
165		2.51	462
166		2.76	565
167		2.55	504

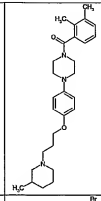
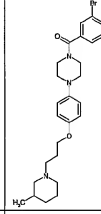
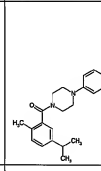
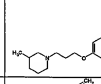
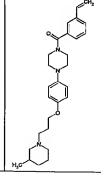
168		2.51	464
169		2.67	490
170		2.45	480
171		2.57	504 506
172		2.63	478
173		2.65	494

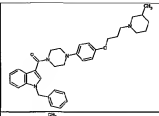
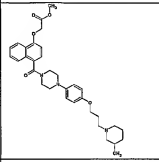
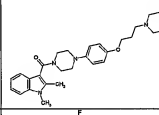
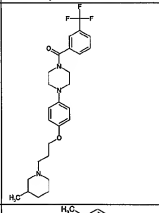
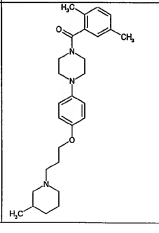
174		2.69	478
175		2.56	482
176		2.49	500 502
177		2.66	478

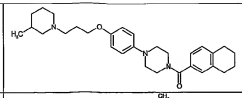
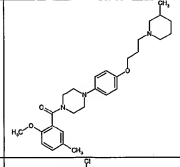
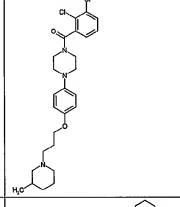
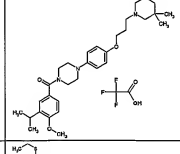
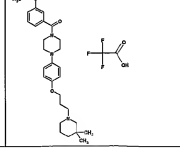
178		2.55	514 516
179		2.47	448
180		2.72	551
181		2.52	560
182		2.47	489

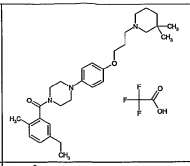
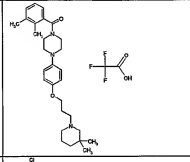
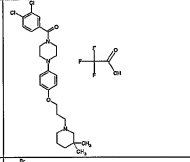
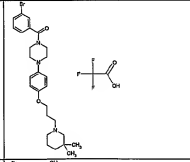
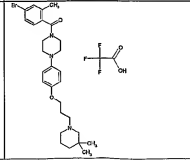
183		2.54	490
184		2.47	450
185		2.60	476
186		2.39	466
187		2.53	491

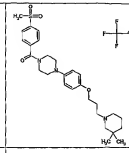
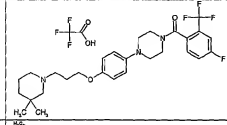
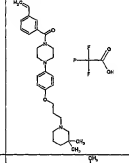
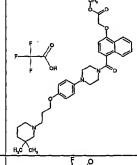
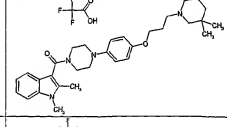
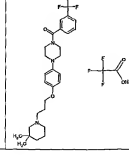
188		2.63	478
189		2.64	494
190		2.68	478
191		2.58	482
192		2.55	464

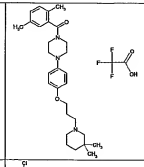
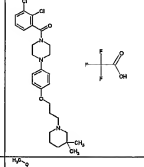
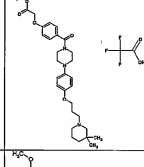
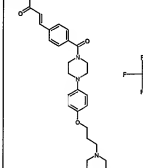
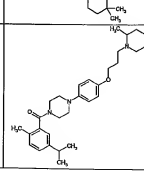
193		2.44	450
194		2.47	500 502
195		2.66	478
196		2.44	508
197		2.44	448

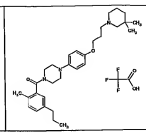
198		2.71	551
199		2.52	560
200		2.46	489
201		2.50	490
202		2.46	450

203		2.62	476
204		2.39	466
205		2.52	490 492
206		2.40	508
207		2.37	496

208		2.35	478
209		2.27	464
210		2.37	504 506
211		2.26	514 516
212		2.34	528 530

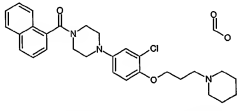
213		2.00	514
214		2.28	522
215		2.26	462
216		2.57	574
217		2.30	503
218		2.30	504

219		2.29	464
220		2.31	504 506
221		2.09	524
222		2.26	520
223		2.77	506

224		2.49	492

Example 225

1-[3-Chloro-4-(3-piperidin-1-ylpropoxy)phenyl]-4-(1-naphthoyl)piperazine formate (E225)



E225a: *tert*-Butyl 4-(1-naphthoyl)piperazine-1-carboxylate

1-Naphthoyl chloride (2.15 ml) was added to a solution of *tert*-butyl piperazine-1-carboxylate (3.28 g) and diisopropylethylamine (3.44 ml) in dichloromethane (100 ml) at 0 °C. After 2 h stirring the mixture was partitioned between dichloromethane and 2M hydrochloric acid. The organic phase was washed with sat. aq. sodium bicarbonate solution, dried ($MgSO_4$) and evaporated to dryness to give *the title compound* (4.9 g) LCMS RT = 3.16 min.

E225b: 1-(1-Naphthoyl)piperazine

tert-Butyl 4-(1-naphthoyl)piperazine-1-carboxylate (E225a) (4.2 g) was dissolved in dichloromethane (80 ml) and treated with trifluoroacetic acid (10 ml) for 4.5 h at 20 °C. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane and 2M sodium hydroxide. The organic phase was dried ($MgSO_4$) and evaporated to dryness to give *the title compound* (3.19 g) LCMS RT = 1.50 min.

E225c: 2-Chloro-4-[4-(1-naphthoyl)piperazin-1-yl]phenol

A mixture of 1-(1-naphthoyl)piperazine (E225b) (143.7 mg), 4-bromo-2-chlorophenol (207 mg), tris(dibenzylideneacetone) dipalladium (4.75 mg), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (4.91 mg) was dissolved in tetrahydrofuran (3 ml) and then treated at 0 °C with 1M solution of lithium bis(trimethylsilyl)amide (1.1 ml) under nitrogen. The mixture was heated to 70 °C for 18 h and then partitioned between water and dichloromethane. The organic phase was separated using hydrophobic frit, and purified on a silica SPE bond elut cartridge eluting with aq. ammonia-methanol-dichloromethane (1:2:98) to give *the title compound* (81 mg) LCMS RT = 3.16 min.

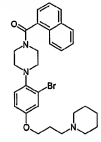
E225d: 1-[3-Chloro-4-(3-piperidin-1-ylpropoxy)phenyl]-4-(1-naphthoyl)piperazine formate

2-Chloro-4-[4-(1-naphthoyl)piperazin-1-yl]phenol (E225c) (37 mg), caesium carbonate (81 mg), sodium iodide (2.3 mg), 1-(3-chloropropyl)piperidine (22 mg) in DMF (2.5 ml)

were heated in a microwave oven at 160 °C for 10 min and at 170 °C for 20 min. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$), and purified by mass directed auto-preparative HPLC to give *the title compound* (30mg) LCMS RT = 2.60 min, ES+ve m/z 492 and 494.

Example 226

1-(2-Bromo-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-4-(1-naphthalenylcarbonyl)piperazine (E226)



E226a: 4-(4-Acetylpiperazin-1-yl)-3-bromophenyl acetate

4-(4-Acetylpiperazin-1-yl)phenol (38.5 g) in dichloromethane (875 ml) was treated with triethylamine (35 ml) and the solution was cooled in ice. Acetyl chloride (15.05 ml) in dichloromethane (87 ml) was added dropwise with stirring, keeping the temperature between 18 and 20°. After 30 min, the solution was washed with water, dried and evaporated to give 4-(4-acetylpiperazin-1-yl)phenyl acetate (44.2 g). A portion of this (31.4 g) was dissolved in acetic acid (720 ml) and sodium acetate (19.7 g) was added. The solution was cooled to 15°, and bromine (6.2 ml) in acetic acid (72 ml) was added dropwise with stirring over 15 min, keeping the temp. at 15°C. After 30min, aqueous sodium metabisulphite solution (4.6 g in 60 ml water) was added and the mixture was concentrated by evaporation to ca. 200 ml. Dichloromethane (500 ml) was added, followed by sodium bicarbonate solution until the pH of the aqueous layer was 5. The dichloromethane layer was diluted (1L) and separated, washed with an equal volume of water, dried, evaporated and purified by chromatography on Biotage (800 g cartridge) eluting with ethyl acetate-hexane (3:1) to give *the title compound*. (34.8 g) mp 75°C.

E226b: 4-(4-Acetylpiperazin-1-yl)-3-bromophenol

A solution of 4-(4-acetylpiperazin-1-yl)-3-bromophenyl acetate (E226a) (29.5 g) in methanol (300 ml) was cooled in an ice bath to 15°C and treated dropwise with 2N NaOH aqueous solution (87 ml). After 30min, the solution was poured into ice-water (1.7 L) and the mixture acidified to pH 6. The white precipitate was collected by filtration and washed with water (0.5 L). Drying under vacuum gave *the title compound* (22.8 g), mp 212-4°C.

E226c: 1-(2-Bromo-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine

A mixture of 4-(4-acetyl-1-piperazinyl)-3-bromophenol (E226b) (1 g) in DMF (10 ml) and chloropropyl piperidine hydrochloride (0.72 g), Cs_2CO_3 (2.99 g), and NaI (75 mg) was heated at 80 °C for 24 h. The mixture was cooled to room temperature and quenched

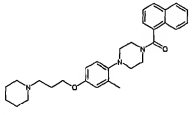
with water (10 ml), then extracted with ethyl acetate and evaporated. The residue was treated with 5 ml of conc. HCl and 5 ml of water and heated to reflux. The reaction mixture was cooled to 20 °C and diluted with water (10 ml), basified with solid potassium carbonate and extracted with DCM. The residue was purified by chromatography on biotage (40 g cartridge) eluting with DCM-EtOH-NH_3 (45:5:1) to give *the title compound* (0.86 g) LCMS RT = 1.68 min, ES+ve m/z 382, 384 $(M+H)^+$.

E226d: 1-{2-Bromo-4-[[3-(1-piperidinyl)propyl]oxy}phenyl)-4-(1-naphthalenylcarbonyl)piperazine

A solution of 1-(2-bromo-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E226c) (0.86 g) in anhydrous DCM (10 ml) and triethylamine (0.34 ml) was cooled to 0°C and naphthoyl chloride (0.37 ml) was added. The mixture was stirred under nitrogen for 48 h, evaporated to dryness and partitioned between saturated sodium bicarbonate solution and DCM. The organic phase was separated, concentrated and the residue was purified by chromatography on biotage (40 g cartridge) eluting with DCM-MeOH-aqueous NH_3 (200:8:1) to afford the title compound (1.2 g). LCMS RT = 2.71 min, ES+ve m/z 536, 538 $(M+H)^+$.

Example 227

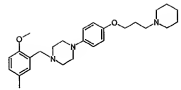
1-(2-Methyl-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-4-(1-naphthalenylcarbonyl) piperazine (E227)



A solution of 1-(2-bromo-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-4-(1-naphthalenylcarbonyl)piperazine (E226) (50 mg), tetrakis(triphenylphosphine) palladium (0) (10 mg), potassium carbonate (38 mg) and trimethylboroxine (23 mg) in of DMF (1 ml) was heated at 150°C in a microwave oven for 10min, cooled, evaporated to dryness and purified by chromatography on a biotage cartridge eluting with DCM-MeOH-aqueous NH_3 (200:8:1) to afford the title compound (21 mg). LCMS RT = 2.63 min, 472 $(M+H)^+$.

Example 228

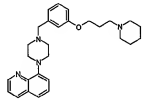
1-{[5-Methyl-2-(methyloxy)phenyl]methyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine formate (E228)



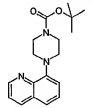
A solution of 5-methyl-2-(methyloxy)benzaldehyde (40 mg) and 1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine [D11] (40mg) in dichloromethane (2 ml) was treated with acetic acid (7.9 µl) and sodium triacetoxyborohydride (56 mg). The resulting suspension was stirred at 22 °C for 24 h. The reaction mixture was concentrated and purified by mass directed auto preparative HPLC to give *the title compound* (4.8mg). LCMS RT = 1.99 min, 438 (MH^+).

Example 229

8-{4-[(3-{[3-(1-Piperidinyl)propyl]oxy}phenyl)methyl]-1-piperazinyl}quinoline trifluoroacetate (E229)



E229a: 1,1-Dimethylethyl 4-(8-quinolinyl)-1-piperazinecarboxylate



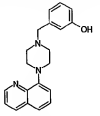
A solution of 8-bromoquinoline (28.6 mg) in dry THF (1 mL) was treated with 1,1-dimethylethyl 1-piperazinecarboxylate (30.7 mg), tris(dibenzylidineacetone) dipalladium (0) (1.5 mg) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (1.6 mg). The reaction mixture was treated with lithium bis(trimethylsilyl)amide (1M in THF, 0.27 mL) and then heated at 75 °C for 4 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by chromatography (silica SPE bond elut cartridge), eluting with a gradient between cyclohexane and EtOAc to give *the title compound* (29 mg). LCMS RT= 2.86 min.

E229b: 8-(1-Piperazinyl)quinoline

A solution of 1,1-dimethylethyl 4-(8-quinolinyl)-1-piperazinecarboxylate (E229a) (2.5 g) in DCM (60 mL) was treated with TFA (20 mL) and stirred at room temperature for 4 h prior

to pouring into DCM and washing with saturated $NaHCO_{3\,(Aq)}$. The organic phase was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (silica SPE cartridge), eluting with gradient between DCM and 100:10:1 DCM-MeOH- aqueous NH_3) to give *the title compound* (643 mg). LCMS RT= 0.68 min.

E229c: 3-{[4-(8-Quinolinyl)-1-piperazinyl]methyl}phenol



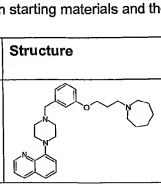
A solution of 8-(1-piperazinyl)quinoline (E229b) (126 mg) in dry DCM (2 mL) was treated with AcOH (500 μL). A solution of 3-hydroxybenzaldehyde (88 mg) in dry DCM (3 mL) was added followed by sodium borohydride (191 mg). The reaction mixture was stirred for 16 h prior to the addition of water. The aqueous phase was neutralised with 2N NaOH. The organic phase was extracted twice with DCM and the combined organic phase concentrated *in vacuo*. The residue was purified by chromatography (silica SPE) eluting with a gradient between DCM and 100:10:1 DCM-MeOH-aqueous NH_3) to give *the title compound* (133 mg). LCMS RT= 1.96 min.

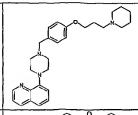
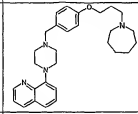
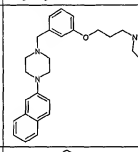
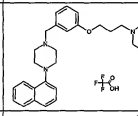
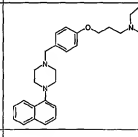
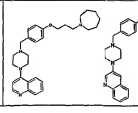
E229d: 8-{4-[(3-{[3-(1-Piperidinyl)propyl]oxy}phenyl)methyl]-1-piperazinyl}quinoline trifluoroacetate

A solution of 1-(3-chloropropyl)piperidine hydrochloride (46 mg) in dry DMF was treated with a solution of 3-{[4-(8-quinolinyl)-1-piperazinyl]methyl}phenol (E229c) (43 mg). The resultant solution was treated with sodium hydride (60% oil dispersion, 11 mg) and stirred at room temperature for 16 h. The reaction mixture was quenched with water (1 drop) and partitioned between water and DCM. The organic phase was concentrated *in vacuo*. The residue was purified by mass directed auto-preparative HPLC to give *the title compound* (5.7 mg). LCMS RT= 1.83 min, ES+ve m/z 445 $(MH)^+$

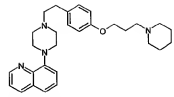
Examples 230-236

Examples 230-236 were prepared in an analogous manner to that described for E229d from known starting materials and those indicated in the table below:

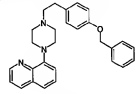
Example	Structure	Starting Materials	RT (min)	Mass ion $(M+H)^+$
230		D30	1.86	458

231		D30	1.78	444
232		D30	1.82	458
233		D28	3.59	457
234		D29	2.18	457
235		D32	2.14	457
236		D31	1.67 &1.89	459 & 459

Example 237
8-{4-[2-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)ethyl]-1-piperazinyl}quinoline trifluoroacetate (E237)

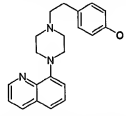


E237a: 8-[4-(2-{4-[(Phenylmethyl)oxy]phenyl}ethyl)-1-piperazinyl]quinoline



A solution of 8-(1-piperazinyl)quinoline (E229b) (126 mg) in dry DMF (2 mL) was treated with diisopropylethylamine (176 μL) followed by a solution of 1-(2-bromoethyl)-4-[(phenylmethyl)oxy]benzene (277 mg) in dry DMF (1 mL). The resultant reaction mixture was stirred under nitrogen for 18 h prior to quenching with water. The reaction mixture was partitioned between water and DCM and the organic phase dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica SPE, eluting with a gradient between DCM and 100:10:1 DCM-MeOH-aqueous NH_3 to give *the title compound* (51 mg). LCMS RT= 2.54 min.

E237b: 4-{2-[4-(8-Quinolinyl)-1-piperazinyl]ethyl}phenol



A solution of 8-[4-(2-{4-[(phenylmethyl)oxy]phenyl}ethyl)-1-piperazinyl]quinoline (E237a) (107 mg) in dry DCM (5 mL) was cooled to -20°C and treated with a solution of boron tribromide (1M in DCM, 250μL). The reaction mixture was stirred at -20°C for 30 min and at room temp. for 12 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica SPE eluting with a gradient between DCM and 100:10:1 DCM-MeOH-aqueous NH_3) to give *the title compound* (51 mg). LCMS RT= 1.73 min.

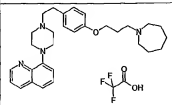
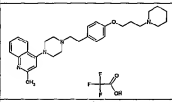
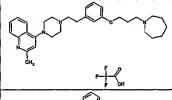
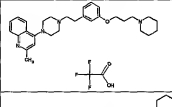
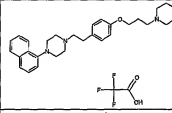
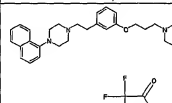
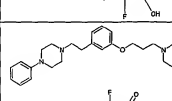
E237c: 8-{4-[2-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)ethyl]-1-piperazinyl}quinoline trifluoroacetate

Was prepared using the method described in E228d LCMS RT = 2.32 min, ES+ve m/z 460 $(M+H)^+$.

Examples 238-244

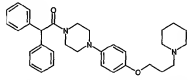
Examples 238-244 were prepared in an analogous manner to that described for E229d from known starting materials and those indicated in the table below:

Example	Structure	Starting	RT	Mass ion

		Materials	(min)	$(M+H)^+$
238		E237b	2.19	474
239		D38	1.68	474
240		D39	1.73	486
241		D39	1.75	473
242		D40	1.82	459
243		D41	3.01	459
244		D42	2.15	408

Example 245

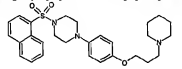
1-Diphenylacetyl-4-[4-(3-piperidin-1-ylpropoxy)phenyl] piperazine (E245)



A solution of diphenylacetic acid (11 mg, 50 μmol) in DMF (1 ml) was treated with a solution of 1-[4-(3-piperidin-1-ylpropoxy)phenyl]piperazine (D11) (15 mg) in DMF (1 ml), followed by triethylamine (20 μl) and HBTU (19 mg). The mixture was shaken for 5 min then left to stand at room temperature overnight. Polystyryl-trisamine (100 μmol) and polystyryl-isocyanate (50 μmol) were added and the mixture shaken for a further 20 h. The mixture was then filtered and the filtrate loaded onto a solid phase cation exchange (SCX) cartridge. After washing with 80% MeOH-DCM, the product was eluted with a solution of NH_3 in MeOH (0.5 M). The eluted fraction was concentrated to dryness under vacuum giving *the title compound* (17.5 mg). LCMS RT = 3.36 min, ES+ve m/z 498 $(M+H)^+$.

Example 246

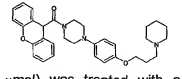
1-(Naphthalen-1-ylsulfonyl)-4-[4-(3-piperidin-1-ylpropoxy)phenyl] piperazine (E246)



A solution of 1-[4-(3-piperidin-1-ylpropoxy)phenyl]piperazine (D11) (30 mg) in DCM (3 ml) was treated with a solution of naphthalene-1-sulfonyl chloride (27 mg) in DCM (1 ml). Polystyryl-methylmorpholine (200 μmol) was added and the mixture shaken at room temperature for 24 h. The mixture was loaded onto a SCX cartridge and after washing with 50% MeOH-DCM, the crude product was eluted with a solution of NH_3 in MeOH (0.5 M). The eluted fraction was concentrated to dryness under vacuum and purified by flash silica chromatography, eluting with 5% MeOH-DCM, to give *the title compound* (22 mg). LCMS RT = 3.30 min, ES+ve m/z 394 $(M+H)^+$.

Example 247

1-(9*H*-Xanthen-9-ylcarbonyl)-4-[4-(3-piperidin-1-ylpropoxy)phenyl] piperazine (E247)

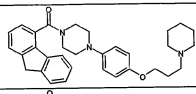
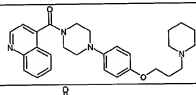
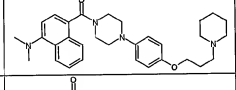
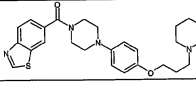


Polystyryl-carbodiimide (450 μmol) was treated with a solution of 9*H*-xanthene-9-carboxylic acid (34 mg) in DMF (2 ml) and shaken for 5 min then treated with a solution of 1-[4-(3-piperidin-1-ylpropoxy)phenyl]piperazine (D11) (30 mg) in DMF (1 ml) and shaken at room temperature for 20 h. Polystyryl-isocyanate (100 μmol) was added and the mixture shaken for a further 24 h. The mixture was then filtered and the filtrate loaded onto a SCX cartridge. After washing with 80% MeOH-DCM, the crude product

was eluted with a solution of NH_3 in MeOH (0.5 M). The eluted fraction was concentrated to dryness under vacuum and purified by flash silica chromatography, eluting with 5-10% MeOH-DCM gradient, to give *the title compound* (5.7 mg). LCMS RT = 3.16 min, ES+ve m/z 512 $[M+H]^+$.

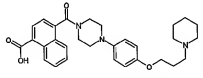
Examples 248-251

Examples 248-251 were prepared according to the procedure for Example 247.

Example	Structure	RT (min)	Mass ion $(M+H)^+$
248		3.08	496
249		1.98	459
250		2.24	501
251		2.14	465

Example 252

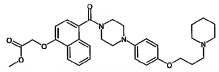
1-(4-Carboxy-1-naphthoyl)-4-[4-(3-piperidin-1-ylpropoxy)phenyl] piperazine di(trifluoroacetate) (E252)



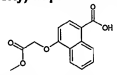
A solution of 1,4-dinaphthoic acid (50 mg) in DMF (2 ml) was treated with a solution of 1-[4-(3-piperidin-1-ylpropoxy)phenyl]piperazine (D11) (70 mg) in DMF (1.5 ml) followed by HBTU (88 mg). The mixture was shaken for 5 min then left to stand at room temperature overnight. Water (100 µl) was added, then the mixture was concentrated to dryness under vacuum and purified using reverse phase HPLC, affording *the title compound* (80 mg). LCMS RT = 2.36 min. ES+ve m/z 502 $[M+H]^+$.

Example 253

1-[4-(Methoxycarbonylmethoxy)naphth-1-oyl]-4-[4-(3-piperidin-1-ylpropoxy)phenyl] piperazine (E253)



E253a: 4-(Methoxycarbonylmethoxy) naphthalene-1-carboxylic acid



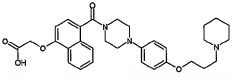
To a solution of methyl (4-formylnaphthalen-1-yloxy) acetate (*J. Med. Chem.* **2002**, *45*, 5755) (2.35 g) in t-BuOH (10 ml), acetone (10 ml), and H_2O (5 ml) at 0 °C were added solid $NaClO_2$ (1.30 g) and $NaH_2PO_4.H_2O$ (1.99 g) and the mixture was stirred at room temperature under nitrogen overnight. Further $NaClO_2$ (1.73 g) and Na_3PO_4 (2.66 g) dissolved in H_2O (3 ml) were added and the reaction continued for 24 h. The mixture was then concentrated under vacuum and treated with H_2O. The resultant precipitate was collected by filtration, washed with H_2O, and dried under vacuum to give *the title compound* (2.2 g). ^{1}H-NMR δ (DMSO- d_6, 400 MHz) 12.74 (br. s, 1H), 8.97 (d, 1H), 8.27 (d, 1H), 8.13 (d, 1H), 7.63 (m, 1H), 7.58 (m, 1H), 6.95 (d, 1H), 5.07 (s, 2H), 3.70 (s, 3H).

E253b: 1-[4-(Methoxycarbonylmethoxy)naphth-1-oyl]-4-[4-(3-piperidin-1-ylpropoxy)phenyl] piperazine

The title compound was prepared from 4-(methoxycarbonylmethoxy) naphthalene-1-carboxylic acid (E253a) (50 mg) and 1-[4-(3-piperidin-1-ylpropoxy)phenyl]piperazine (D11) (58 mg) according to the procedure for Example 252 (76 mg). LCMS RT = 2.79 min, ES+ve m/z 545 $[M+H]^+$.

Example 254

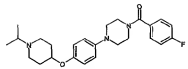
1-[4-(Carboxymethoxy)naphth-1-oyl]-4-[4[(3-piperidin-1-ylpropoxy)phenyl] piperazine (E254)



A stirred solution of 1-[4-(methoxycarbonylmethoxy)naphth-1-oyl]-4-[4-(3-piperidin-1-ylpropoxy)phenyl] piperazine (E253b) (38 mg) in THF (2 ml) was treated with a solution of KOH (6 mg) in H_2O (1 ml). After 1.5 h the mixture was treated with a solution of 2M HCl in Et_2O (50 µl) and concentrated to dryness under vacuum. The residue was treated with EtOH, then filtered and the filtrate concentrated to dryness under vacuum to give *the title compound* (29 mg). LCMS RT = 2.42 min, ES+ve m/z 532 $[M+H]^+$.

Example 255

1-[(4-Fluorophenyl)carbonyl]-4-(4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)piperazine (E255)



Step 1: 4-{4-[(4-Fluorophenyl)carbonyl]-1-piperazinyl}phenol

4-Fluorobenzoylchloride (1.59 ml, 18.5 mmol) in dichloromethane (15 ml) was added to an ice cooled mixture of 4-(1-piperazinyl)phenol (3 g, 16.8 ml) and triethylamine (2.8 ml, 20.2 mmol). The resulting mixture was stirred at room temperature for 18 hours. The solvent was removed by evaporation and the residue dissolved in methanol (30 ml). This was treated with potassium carbonate (5 g) for 30 minutes and filtered. The filtrate was evaporated and dissolved in ethyl acetate. This solution was washed with saturated sodium hydrogen carbonate solution, dried (sodium sulphate) and evaporated to give a pink solid (2.58g, 51%) MS (ES+) m/e 301 $[M+H]^+$.

Step 2: 1,1-Dimethylethyl 4-[(4-{4-[(4-fluorophenyl)carbonyl]-1-piperazinyl}phenyl)oxy]-1-piperidinecarboxylate

Di-*tert*-butyl azodicarboxylate (2.4 g, 10.3 mmol) was added to a mixture of 4-{4-[(4-fluorophenyl)carbonyl]-1-piperazinyl}phenol (2.57g, 8.6 mmol), triphenyl phospine (2.7 g, 10.3 mmol) and 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate (2 g, 10.3 mmol) in tetrahydrofuran (30 ml). The mixture was stirred at room temperature for 18 hours. The reaction was diluted with ethyl acetate and washed with 2 molar sodium hydroxide solution. The organic portion was dried (sodium sulphate) and evaporated. The residue was purified on a silica gel column eluting with a mixture of hexane:ethyl acetate (1:1) to afford the title compound (2.75 g, 67%) MS (ES+) m/e 484 $[M+H]^+$.

Step 3: 1-[(4-Fluorophenyl)carbonyl]-4-[4-(4-piperidinyloxy)phenyl]piperazine

A solution of 1,1-dimethylethyl 4-[(4-{4-[(4-fluorophenyl)carbonyl]-1-piperazinyl}phenyl)oxy]-1-piperidinecarboxylate (2.75 g, 5.7 mmol) in trifluoroacetic acid (10 ml) was stirred at room temperature for 30 minutes. The solvent was removed by evaporation and the residue purified on SCX ion exchange resin eluting with methanol and then a mixture of 0.88 ammonia:methanol (1:9) to afford the title compound (2.1 g, 95%) MS (ES+) m/e 384 $[M+H]^+$.

Step 4: 1-[(4-Fluorophenyl)carbonyl]-4-(4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)piperazine

Sodium triacetoxyborohydride (360 mg, 1.72 mmol) was added to a solution of 1-[(4-fluorophenyl)carbonyl]-4-[4-(4-piperidinyloxy)phenyl]piperazine (330 mg, 0.86 mmol) and acetone (126 µl, 1.72 mmol) in dichloromethane (5 ml). After stirring at room temperature for 18 hours, with 2 molar sodium hydroxide solution was added and the mixture extracted with ethyl acetate. The extracts were dried (sodium sulphate) and evaporated. The residue was purified on a silica gel column eluting with a mixture of methanol: 0.88 ammonia:methanol:dichloromethane (0.5:4.5:95) to afford the title compound (191 mg, 52%) MS (ES+) m/e 426 $[M+H]^+$.

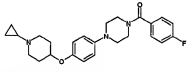
Examples 256-259

Examples 256-259 were prepared in the same manner as Example 255 using the appropriate ketone or aldehyde as indicated in the table:

Compound	Ketone/Aldehyde	MS (ES+) m/e $[M+H]^+$.
1-(4-{[1-(Cyclopropylmethyl)-4-piperidinyl]oxy}phenyl)-4-[(4-fluorophenyl)carbonyl]piperazine (E256)	cyclopropane carbaldehyde	475
1-[(4-Fluorophenyl)carbonyl]-4-(4-{[1-(2-methylpropyl)-4-piperidinyl]oxy}phenyl)piperazine (E257)	2-methylpropanal	440
1-{4-[(1-Cyclopentyl-4-piperidinyl)oxy]phenyl}-4-[(4-fluorophenyl)carbonyl]piperazine (E258)	cyclopentanone	452
1-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]phenyl}-4-[(4-fluorophenyl)carbonyl]piperazine (E259)	cyclobutanone	438

Example 260

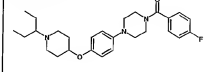
1-{4-[(1-Cyclopropyl-4-piperidinyl)oxy]phenyl}-4-[(4-fluorophenyl)carbonyl] piperazine (E260)

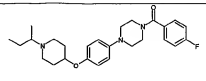


{[1-(ethyloxy)cyclopropyl]oxy}(trimethyl)silane 524 µl, 2.6 mmol) was added to a stirring mixture of the product of Example 255, step 3 (1-[(4-fluorophenyl)carbonyl]-4-[4-(4-piperidinyloxy)phenyl]piperazine) (250 mg, 0.65 mmol) and polymer bound cyanoborohydride (650 mg of 4 mmol/g resin) in methanol (10 ml) and acetic acid (250 µl).This mixture was heated at 50 °C for 18 hours. The mixture was filtered and the filtrate evaporated. The residue was purified on a silica cartridge eluting with a mixture of: 0.88 ammonia:methanol:dichloromethane (0.5:4.5:95) to afford the title compound (155 mg, 56%) MS (ES+) m/e 424 $[M+H]^+$.

Examples 261-262

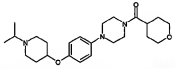
Examples 261-262 may be prepared in an analogous manner to that described in Example 255, step 4 from pentan-3-one and the product of Example 255, step 3.

Compound	Structure
1-(4-{4-[1-(1-Ethyl-propyl)-piperidin-4-yloxy]-phenyl}-piperazin-1-yl)-1-(4-fluoro-phenyl)-methanone (E261)	

1-{4-[4-(1-sec-Butyl-piperidin-4-yloxy)-phenyl]-piperazin-1-yl}-1-(4-fluoro-phenyl)-methanone (E262)	

Example 263

1-(4-{[1-(1-Methylethyl)-4-piperidinyl]oxy}phenyl)-4-(tetrahydro-2H-pyran-4-ylcarbonyl)piperazine (E263)



Step 1: 1,1-Dimethylethyl 4-[(4-iodophenyl)oxy]-1-piperidinecarboxylate

Di-*tert*-butyl azodicarboxylate (5.9 g, 25.8 mmol) was added to a mixture of 4-iodophenol (4.72 g, 21.5 mmol), triphenyl phospine (6.8 g, 25.8 mmol) and 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate (5.18 g, 25.8 mmol) in tetrahydrofuran (100 ml). The mixture was stirred at room temperature for 18 hours. The reaction was diluted with ethyl acetate and washed with 2 molar sodium hydroxide solution. The organic portion was dried (sodium sulphate) and evaporated. The residue was purified on a silica column eluting with 9-1 hexane-ethyl acetate to afford the title compound (5.5 g, 64%) MS (ES+) m/e 304 $[M+H]^+$-BOC.

Step 2: 4-[(4-Iodophenyl)oxy]piperidine

Product of Step 1 (1,1-dimethylethyl 4-[(4-iodophenyl)oxy]-1-piperidinecarboxylate) (5.5 g, 13.6 mmol) in trifluoroacetic acid (10 ml) was stirred at room temperature for 30 minutes. The solvent was removed by evaporation and the residue basified using 2M sodium hydroxide solution. This was extracted into dichloromethane, the extracts were dried (sodium sulphate) and evaporated to afford the title compound (3.4 g, 82%) MS (ES+) m/e 304 $[M+H]^+$.

Step 3: 4-[(4-Iodophenyl)oxy]-1-(1-methylethyl)piperidine

Sodium triacetoxyborohydride (4.75 mg, 22.4 mmol) was added to a solution of the product of Step 2 (4-[(4-iodophenyl)oxy]piperidine) (3.4 g, 11.2 mmol) and acetone (1.65 ml, 22.4 mmol) in dichloromethane (70 ml). After stirring at room temperature for 18 hours, 2 molar sodium hydroxide solution was added and the mixture extracted with ethyl acetate. The extracts were dried (sodium sulphate) and evaporated to afford the title compound (3.63 mg, 94%) MS (ES+) m/e 346 $[M+H]^+$.

Step 4: 1,1-Dimethylethyl 4-(4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)-1-piperazinecarboxylate

A mixture of palladium acetate (32 mg, 5 mol%) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (135 mg, 7.5 mol%) in toluene was heated at 100 °C for 10 minutes. A solution of the product of Step 3 (4-[(4-iodophenyl)oxy]-1-(1-methylethyl)piperidine) (1 g, 2.9 mmol) and 1,1-dimethylethyl 1-piperazinecarboxylate (647 mg, 3.5 mmol) in toluene (10 ml) was added followed by sodium *tert*-butoxide (390 mg, 4.4 mmol). This mixture was heated at 100 °C for 3 hours and filtered through kieselghur. The filtrate was

evaporated and purified on a silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.3:2.7:97) to furnish the title compound (770 mg, 66%) MS (ES+) m/e 404 $[M+H]^+$.

Step 5: 1-(4-{[1-(1-Methylethyl)-4-piperidinyl]oxy}phenyl)piperazine

A solution of the product of Step 5 (1,1-dimethylethyl 4-(4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)-1-piperazinecarboxylate) (750 mg, 1.86 mmol) in trifluoroacetic acid (4 ml) was stirred at room temperature for 30 minutes. The solvent was removed by evaporation and the residue purified on SCX ion exchange resin eluting with methanol and then 10% of 0.88 ammonia solution in methanol to furnish the title compound (514 mg, 91%) MS (ES+) m/e 304 $[M+H]^+$.

Step 6: 1-(4-{[1-(1-Methylethyl)-4-piperidinyl]oxy}phenyl)-4-(tetrahydro-2H-pyran-4-ylcarbonyl)piperazine

A mixture of polymer bound cyclohexyl carbodiimide (460 mg of 1.9 mmol/g resin), tetrahydro-2*H*-pyran-4-carboxylic acid (111 mg, 0.86 mmol) and 1*H*-1,2,3-benzotriazol-1-ol (116 mg, 0.86 mmol) in dichloromethane (10 ml). After 20 minutes the product of Step 5 (1-(4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)piperazine) (128 mg, 0.46 mmol) was added and the mixture stirred for 60 minutes. The mixture was evaporated and the residue was purified on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.3:2.7:97) to furnish the title compound (134 mg, 75%) MS (ES+) m/e 416 $[M+H]^+$.

Examples 264-268

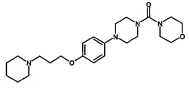
Examples 264 to 268 were prepared in the same manner as Example 263 using the appropriate acid highlighted in the table below:

Compound	Acid	MS (ES+) m/e $[M+H]^+$.
4-{[4-(4-{[1-(1-Methylethyl)-4-piperidinyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzonitrile (E264)	4-cyanobenzoic acid	433
1-(4-{[1-(1-Methylethyl)-4-piperidinyl]oxy}phenyl)-4-(4-pyridinylcarbonyl)piperazine (E265)	Pyridine-4-carboxylic acid	409
1-(4-{[1-(1-Methylethyl)-4-piperidinyl]oxy}phenyl)-4-{[4-(methylsulfonyl)phenyl]carbonyl}piperazine (E266)	4-(methylsulfonyl) benzoic acid	486
1-[(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)carbonyl]-4-(4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)piperazine (E267)	tetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide	464

1-(4-{[1-(1-Methylethyl)-4-piperidinyl]oxy}phenyl)-4-{[4-(1-pyrrolidinylcarbonyl)phenyl]carbonyl} piperazine (E268)	4-(1-pyrrolidinyl carbonyl)benzoic acid (J.Med. Chem., **46(10)**, 1845-1857, 2003)	505

Example 269

4-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}morpholine (E269)



Step 1: 4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinecarbonyl chloride hydrochloride salt

A solution of 1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (D11) (524 mg, 1.73 mmol) in dichloromethane (10 ml) was added drop-wise to 2M solution of phosgene in toluene (1.8 ml). The mixture was stirred at room temperature for 60 minutes and the solvent was removed by evaporation to give a white powder (680 mg) NMR (DMSO) δ 1.4 (2H, m), 1.75(4H, m), 2.2(2H, m), 2.88(2H, m), 3.1-3.9 (12H, m), 4.06(2H, m), 6.89(2H,m), 7.01(2H, m), 9.97(H, m)

Step 2: 4-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}morpholine

Morpholine (75 µl, 1.1 mmol) was added to a mixture of the product of Step 1 (4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinecarbonyl chloride hydrochloride salt) (170 mg, 0.42 mmol) and triethylamine (126 µl, 0.88 mmol) in dichloromethane (5 ml). After 60 minutes the mixture was evaporated and purified on a silica gel eluting with mixture of methanol: 0.88 ammonia: methanol: dichloromethane 0.2:2.8:98) solution to give a white solid (141 mg, 81%) MS (ES+) m/e 417 $[M+H]^+$.

Examples 270-282

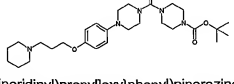
Examples 270 to 282 were prepared in the same manner as Example 269 using the appropriate amine highlighted in the table below.

Compound	Amine	MS (ES+) m/e $[M+H]^+$.
1-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-4-(1-pyrrolidinylcarbonyl)piperazine (E270)	Pyrrolidine	401
1-(1-Piperidinylcarbonyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E271)	Piperidine	415
4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-	Ammonia	347

piperazinecarboxamide (E272)		
4-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}thiomorpholine (E273)	Thiomorpholine	433
4-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}thiomorpholine 1,1-dioxide (E274)	thiomorpholine 1,1-dioxide	465
4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-N-(tetrahydro-2H-pyran-4-yl)-1-piperazinecarboxamide (E275)	tetrahydro-2*H*-pyran-4-amine	431
1-{[(2R,6S)-2,6-Dimethyl-1-piperidinyl]carbonyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E276)	(2*R*,6*S*)-2,6-dimethylpiperidine	443
1-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}-4-piperidinecarboxamide (E277)	4-piperidine carboxamide	458
1-{[(2R,5S)-2,5-Dimethyl-1-pyrrolidinyl]carbonyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E278)	(2*R*,5*S*)-2,5-dimethyl pyrrolidine	429
1-[(2-Phenyl-1-pyrrolidinyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E279)	2-phenyl pyrrolidine	477
1-[(3-Phenyl-1-pyrrolidinyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E280)	3-phenyl pyrrolidine	477
4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-N-6-quinolinyl-1-piperazinecarboxamide (E281)	6-quinolinamine	474
N-(4-Cyanophenyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinecarboxamide (E282)	4-amino benzonitrile	448

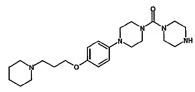
Example 283

1,1-Dimethylethyl 4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}-1-piperazinecarboxylate (E283)



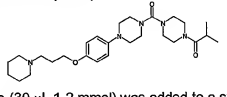
A solution of 1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (D11) (1.8 g, 5.94 mmol) in dichloromethane 15 ml) was added to a 2M solution of phosgene in toluene (6 ml) and stirred for 60 minutes. The solvent was removed by evaporation and the residue dissolved in dichloromethane (30 ml). Triethylamine (1.7 ml, 11.9 mmol) was added followed by 1,1-dimethylethyl 1-piperazinecarboxylate (1.2 g, 6.5 mmol) and the mixture stirred for 90 minutes. The solvent was removed by evaporation and the residue purified on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.5:4.5:95) to furnish the title compound (1.13 g, 37%) MS (ES+) m/e 516 $[M+H]^+$.

Example 284
1-(1-Piperazinylcarbonyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E284)



A solution of 1,1-dimethylethyl 4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}-1-piperazinecarboxylate (E283) (1.13 g, 2.19 mmol) in trifluoroacetic acid (5 ml) and dichloromethane (5 ml) was stirred at room temperature for 90 minutes. The solvent was removed by evaporation and the residue purified an SCX ion exchange resin eluting with methanol and then a mixture of 0.88 ammonia solution:methanol (1:9) to furnish the title compound (854 mg, 94%) MS (ES+) m/e 416 $[M+H]^+$.

Example 285
1-(2-Methylpropanoyl)-4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}piperazine (E285)



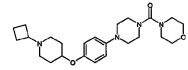
2-methylpropanoyl chloride (30 µl, 1.2 mmol) was added to a stirring mixture of 1-(1-piperazinylcarbonyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E284) (100 mg, 0.24 mmol) and triethylamine (37 µl, 0.26 mmol) in dichloromethane (2 ml). The resulting mixture was stirred at room temperature for 60 minutes. This was evaporated and passed through an SCX ion exchange resin eluting with methanol and then a mixture of 0.88 ammonia solution:methanol (1:9). The basic fractions were evaporated and the residue purified on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.5:4.5:95) to furnish the title compound (50 mg, 43%) MS (ES+) m/e 486 $[M+H]^+$.

Examples 286-291
Examples 286 to 291 were prepared in the same manner as Example 285 using the appropriate acid chloride:

Compound	Acid Chloride	MS (ES+) m/e $[M+H]^+$.
1-(Cyclopropylcarbonyl)-4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}piperazine (E286)	cyclopropanecarbonyl chloride	484

1-(Cyclobutylcarbonyl)-4-[[4-(4-[[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}piperazine (E287)	cyclobutanecarbonyl chloride	497
1-(Cyclopentylcarbonyl)-4-[[4-(4-[[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}piperazine (E288)	cyclopentanecarbonyl chloride	512
1-(Cyclohexylcarbonyl)-4-[[4-(4-[[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}piperazine (E289)	cyclohexanecarbonyl chloride	526
1-(4-[[3-(1-Piperidinyl)propyl]oxy}phenyl)-4-[[4-(tetrahydro-2H-pyran-4-ylcarbonyl)-1-piperazinyl]carbonyl}piperazine (E290)	tetrahydro-2*H*-pyran-4-carbonyl chloride	528
1-[(4-Chlorophenyl)carbonyl]-4-[[4-(4-[[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}piperazine (E291)	4-chlorobenzoyl chloride	555

Example 292
4-[(4-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]phenyl}-1-piperazinyl)carbonyl] morpholine (E292)



Step 1: Phenylmethyl 4-{4-[(1-[[(1,1-dimethylethyl)oxy]carbonyl}-4-piperidinyl)oxy]phenyl}-1-piperazinecarboxylate
A mixture of palladium acetate (300 mg, 5 mol%) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.3 g, 7.5 mol%) in toluene was heated at 100 °C for 10 minutes. A solution of the product of Example 263, step 1 (1,1-dimethylethyl 4-[(4-iodophenyl)oxy]-1-piperidinecarboxylate) (13 g, 59.5 mmol) and phenylmethyl 1-piperazinecarboxylate (20 g, 49.6 mmol) in toluene (120 ml) was added followed by sodium *tert*-butoxide (7.1 g, 64.5 mmol). This mixture was heated at 100 °C for 15 minutes and filtered through kieselghur. The filtrate was evaporated and purified on silica gel eluting with a mixture of hexane:ethyl acetate (2:1) to furnish the title compound (6.4 g, 26%) MS (ES+) m/e 496 $[M+H]^+$.

Step 2: Phenylmethyl 4-[4-(4-piperidinyloxy)phenyl]-1-piperazinecarboxylate
A solution of the product from step 1 (phenylmethyl 4-{4-[(1-[[(1,1-dimethylethyl)oxy]carbonyl}-4-piperidinyl)oxy]phenyl}-1-piperazinecarboxylate) (2 g, 4 mmol) in trifluoroacetic acid (5 ml) and dichloromethane (5 ml) was stirred at room temperature for 45 minutes. The solvent was removed by evaporation and the residue purified an SCX ion exchange resin eluting with methanol and then a mixture of 0.88 ammonia solution:methanol (1:9).methanol. The basic fractions were then reduced *in vacuo* to furnish the title compound (1.53 mg, 97%) MS (ES+) m/e 396 $[M+H]^+$.

Step 3: Phenylmethyl 4-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-1-piperazinecarboxylate

Sodium triacetoxyborohydride (1.64 g, 7.74 mmol) was added to a solution of the product of step 2 (phenylmethyl 4-[4-(4-piperidinyloxy)phenyl]-1-piperazinecarboxylate) (1.53 g, 3.87 mmol) and cyclobutanone (578 µl, 7.74 mmol) in dichloromethane (15 ml). After 2 hours, methanol was added and the mixture evaporated. The residue was passed through an SCX ion exchange resin eluting with methanol and then a mixture of 0.88 ammonia solution:methanol (1:9). The basic fractions were evaporated and the residue purified on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.5:4.5:95) to furnish the title compound (1.35 g, 78%) MS (ES+) m/e 450 $[M+H]^+$.

Step 4: 1-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]phenyl}piperazine

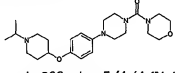
A solution of phenylmethyl 4-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-1-piperazinecarboxylate (1.35 g, 3 mmol) in absolute ethanol 20 ml was hydrogenated at room temperature and pressure over a 50% wet paste of 10% palladium on carbon (500 mg). After 18 hours the catalyst was removed by filtration and the filtrate evaporated to give the title compound (889 mg, 94%) MS (ES+) m/e 316 $[M+H]^+$.

Step 5: 4-[(4-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]phenyl}-1-piperazinyl)carbonyl]morpholine

4-morpholinecarbonyl chloride (78 mg, 0.53 mmol) was added to a mixture of the product from step 4 (1-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}piperazine) (150 mg, 0.48 mmol) and polymer bound diethylamine resin (300 mg of 3.2 mmol/g) in dichloromethane (5 ml). After 2 hours the mixture was filtered and the filtrate evaporated. The residue was residue purified on a silica on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.5:4.5:95) to furnish the title compound (121 mg, 58%) MS (ES+) m/e 429 $[M+H]^+$.

Example 293

4-{[4-(4-{[1-(1-Methylethyl)-4-piperidinyl]oxy}phenyl)-1-piperazinyl]carbonyl}morpholine (E293)



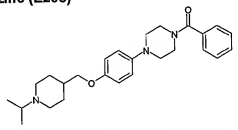
A solution of the product of Example 263, step 5 {1-(4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)piperazine) (200 mg, 0.66 mmol) was added to a 2M solution of phosgene in toluene (1.3 ml) and the mixture stirred for 30 minutes. The solvent was removed by evaporation and the residue dissolved in dichloromethane (5 ml). Morpholine (75 µl, 1.1 mmol) followed by triethylamine (126 µl, 0.88 mmol) were then added. After 60 minutes the mixture was evaporated and purified on a silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.3:2.7:97) to furnish the title compound

(177 mg, 65%) MS (ES+) m/e 417 $[M+H]^+$.

Example 294
1-(4-{[1-(1-Methylethyl)-4-piperidinyl]oxy}phenyl)-4-(1-piperidinylcarbonyl) piperazine (E294)

Example 294 was prepared in the same manner as Example 293 from piperidine. MS (ES+) m/e 415 $[M+H]^+$.

Example 295
1-[4-({[1-(1-Methylethyl)-4-piperidinyl]methyl}oxy)phenyl]-4-(phenylcarbonyl)piperazine (E295)



Step 1: 1,1-Dimethylethyl 4-(hydroxymethyl)-1-piperidinecarboxylate
1-{[(1,1-dimethylethyl)oxy]carbonyl}-4-piperidinecarboxylic acid (2.0g, 8.73mmol) was dissolved in dry tetrahydrofuran (20ml), cooled in an ice bath and treated with 1M borane-tetrahydrofuran solution (17.46ml, 17.46mmol) under argon. The mixture was allowed to warm to ambient temperature and stirred under argon for 4 hours. A solution of methanol (5ml) in tetrahydrofuran (10ml) was added followed by methanol (4ml) and water (2ml). The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution (x2). The organic layer was separated, dried under magnesium sulphate and evaporated *in vacuo* to give the title compound (1.83g). ^{1}H NMR ($CDCl_3$) δ 4.18-4.10 (2H, m), 3.51-3.50 (2H, m), 2.72-2.68 (2H, m), 1.75-1.69 (2H, m), 1.62 (1H, m), 1.46 (9H, s), 1.20-1.10 (2H, m).

Step 2: 1,1-Dimethylethyl 4-(iodomethyl)-1-piperidinecarboxylate
Triphenylphosphine (2.79g, 10.6mmol) was added to a mixture of iodine (2.59g, 10.2mmol) in toluene (90ml). After 5 minutes, pyridine (1.65ml, 20.4mmol) followed by the product from Step 1 was added. The resulting mixture was heated under reflux for 3 hours. The cooled reaction mixture was filtered and the filtrate was washed with saturated sodium thiosulfate and brine, dried under magnesium sulphate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with a mixture of ethyl acetate:hexane (1:9) to give the title compound (1.83g). ^{1}H NMR ($CDCl_3$) δ 4.18-4.10 (2H, m), 3.11-3.09 (2H, d), 2.72-2.65 (2H, m), 1.88-1.82 (2H, m), 1.62 (1H, m), 1.46 (9H, s), 1.20-1.11 (2H, m).

Step 3: 4-[4-(Phenylcarbonyl)-1-piperazinyl]phenol
4-(1-piperazinyl)phenol (4.0g, 22.5mmol) was dissolved in dry dichloromethane (50ml), treated with triethylamine (3.4ml, 24.8mmol) and benzoyl chloride (2.6ml, 22.5mmol) and stirred at ambient temperature under argon for 2 hours. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate. The ethyl acetate layer was washed

with saturated sodium bicarbonate solution, dried under magnesium sulphate and evaporated *in vacuo*. The crude product was dissolved in methanol, treated with potassium carbonate (2 equivalents) and stirred at ambient temperature for 30 minutes. The potassium carbonate was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in ethyl acetate, washed with saturated sodium bicarbonate solution, dried under magnesium sulphate and evaporated *in vacuo* to give the title compound (5.27g). MS(ES+) m/e 283 $[M+H]^+$.

Step 4: 1,1-Dimethylethyl 4-[({4-[4-(phenylcarbonyl)-1-piperazinyl]phenyl}oxy)methyl]-1-piperidine carboxylate

The product from step 2 (1.83g, 5.63mmol), the product from step 3 (1.59g, 5.63mmol), potassium carbonate (1.86g, 13.5mmol) and potassium iodide (2.24g, 13.5mmol) were added together in 2-butanone (70ml) and the mixture heated under reflux for 24 hours. The mixture was allowed to cool to room temperature, treated with sodium thiosulfate (1M, 15ml) and extracted with ethyl acetate. The organic layer was separated, washed with water and brine, dried under magnesium sulphate and evaporated *in vacuo*. The title compound (0.30g) was obtained by silica gel chromatography eluting with a mixture of ethyl acetate:hexane (1:1). MS(ES+) m/e 480 $[M+H]^+$.

Step 5: 1-(Phenylcarbonyl)-4-{4-[(4-piperidinylmethyl)oxy]phenyl}piperazine

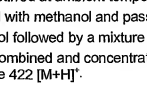
The product from step 4 (0.30g, 0.63mmol) was dissolved in dichloromethane (3ml), treated with trifluoroacetic acid (2ml) and stirred at room temperature under argon for 2 hours. The solvent was removed *in vacuo* and the residue dissolved in methanol and passed down an SCX ion exchange column (5g) eluting with methanol followed by a mixture of 0.880 ammonia:methanol (1:9). The basic fractions were combined and concentrated *in vacuo* to afford the title compound (0.1g); MS(ES+) m/e 380 $[M+H]^+$.

Step 6: 1-[4-({[1-(1-Methylethyl)-4-piperidinyl]methyl}oxy)phenyl]-4-(phenylcarbonyl)piperazine

The product of step 5 (90mg, 0.24mmol) in dry dichloromethane (4ml) was treated with acetone (0.06ml, 0.72mmol) and glacial acetic acid (1 drop) and stirred at ambient temperature for 15 minutes. Sodium triacetoxyborohydride (152mg, 0.72mmol) was added and the reaction mixture stirred at ambient temperature under argon for 36 hours. The reaction mixture was diluted with methanol and passed down an SCX ion exchange column (5g) eluting with methanol followed by a mixture of 0.880 ammonia:methanol (1:9). The basic fractions were combined and concentrated *in vacuo* to afford the title compound (98mg); MS(ES+) m/e 422 $[M+H]^+$.

Example 296

1-[4-({[(3S)-1-(1-Methylethyl)-3-piperidinyl]methyl}oxy)phenyl]-4-(phenylcarbonyl)piperazine (E296)



Step 1: 1,1-Dimethylethyl (3*S*)-3-(hydroxymethyl)-1-piperidinecarboxylate

The title compound was prepared from (3*S*)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-3-piperidinecarboxylic acid using the method of Example 295 step 1. ^{1}H NMR ($CDCl_3$) δ 3.99-3.58 (3H, m), 3.50 (1H, m), 3.22-2.95 (1H, m), 2.80-2.52 (1H, m), 1.87-1.52 (3H, m), 1.46 (9H, s), 1.32-1.12 (1H, m), 0.95-0.92 (1H, q).

Step 2: 1,1-Dimethylethyl (3*S*)-3-(iodomethyl)-1-piperidinecarboxylate

The title compound was prepared from the product of step 1 using the method of Example 295 step 2. ^{1}H NMR ($CDCl_3$) δ 4.11-3.98 (1H, m), 3.87-3.82 (1H, m), 3.09-2.08 (2H, d), 2.85-2.78 (2H, m), 1.93-1.91 (1H, m), 1.66-1.62 (2H, m), 1.47 (10H, s), 1.30-1.22 (1H, m).

Step 3: 1,1-Dimethylethyl (3*S*)-3-[({4-[4-(phenylcarbonyl)-1-piperazinyl]phenyl}oxy)methyl]-1-piperidinecarboxylate

The title compound was prepared from the product of step 2 and the product of Example 295 Step 3 using the method of Example 295 Step 4. MS(ES+) m/e 480 $[M+H]^+$.

Step 4: 1-(Phenylcarbonyl)-4-(4-{[(3*S*)-3-piperidinylmethyl]oxy}phenyl)piperazine

The title compound was prepared from the product of step 3 using the method of Example 295 Step 5. MS(ES+) m/e 380 $[M+H]^+$.

Step 5: 1-[4-({[(3S)-1-(1-Methylethyl)-3-piperidinyl]methyl}oxy)phenyl]-4-(phenylcarbonyl)piperazine

The title compound was prepared from the product of step 4 and acetone using the method of Example 295 Step 6. MS(ES+) m/e 422 $[M+H]^+$

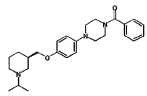
Examples 297-299

The following examples were prepared from the product of Example 296 Step 4 using the method of Example 295 Step 6 with the appropriate ketone or aldehyde as indicated in the table below.

Example	Ketone or Aldehyde	MS (ES+) m/e $[M+H]^+$
1-[4-({[(3S)-1-Cyclopentyl-3-piperidinyl]methyl}oxy) phenyl]-4-(phenylcarbonyl)piperazine (E297)	Cyclopentanone	448
1-[4-({[(3S)-1-(Cyclopropylmethyl)-3-piperidinyl] methyl}oxy)phenyl]-4-(phenylcarbonyl)piperazine (E298)	Cyclopropane carboxaldehyde	434
1-[4-({[(3S)-1-Ethyl-3-piperidinyl]methyl}oxy)phenyl]-4-(phenylcarbonyl)piperazine (E299)	Acetaldehyde	408

Example 300

1-[4-({[(3R)-1-(1-Methylethyl)-3-piperidinyl]methyl}oxy)phenyl]-4-(phenylcarbonyl)piperazine (E300)



Step 1: 1,1-Dimethylethyl (3*R*)-3-(hydroxymethyl)-1-piperidinecarboxylate

The title compound was prepared from (3*R*)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-3-piperidinecarboxylic acid using the method of Example 295 step 1. ^{1}H NMR ($CDCl_3$) δ 3.99-3.58 (3H, m), 3.50 (1H, m), 3.22-2.95 (1H, m), 2.80-2.52 (1H, m), 1.87-1.52 (3H, m), 1.46 (9H, s), 1.32-1.12 (1H, m), 0.95-0.92 (1H, q).

Step 2: 1,1-Dimethylethyl (3*R*)-3-(iodomethyl)-1-piperidinecarboxylate

The title compound was prepared from the product of step 1 using the method of Example 295 step 2. ^{1}H NMR ($CDCl_3$) δ 4.11-3.98 (1H, m), 3.87-3.82 (1H, m), 3.09-2.08 (2H, d), 2.85-2.78 (2H, m), 1.93-1.91 (1H, m), 1.66-1.62 (2H, m), 1.47 (10H, s), 1.30-1.22 (1H, m).

Step 3: 1,1-Dimethylethyl (3*R*)-3-[({4-[4-(phenylcarbonyl)-1-piperazinyl]phenyl}oxy)methyl]-1-piperidinecarboxylate

The title compound was prepared from the product of step 2 and the product of Example 295 Step 3 using the method of Example 295 Step 4. MS(ES+) m/e 480 $[M+H]^+$.

Step 4: 1-(Phenylcarbonyl)-4-(4-{[(3*R*)-3-piperidinylmethyl]oxy}phenyl)piperazine

The title compound was prepared from the product of step 3 using the method of Example 295 Step 5. MS(ES+) m/e 380 $[M+H]^+$.

Step 5: 1-[4-({[(3R)-1-(1-Methylethyl)-3-piperidinyl]methyl}oxy)phenyl]-4-(phenylcarbonyl)piperazine

The title compound was prepared from the product of step 4 and acetone using the method of Example 295 Step 6. MS(ES+) m/e 422 $[M+H]^+$

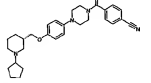
Examples 301-302

The following examples were prepared from the product of Example 300 Step 4 using the method of Example 295 Step 6 using the appropriate aldehyde or ketone as indicated.

Example	Ketone or Aldehyde	MS (ES+) m/e $[M+H]^+$
1-[4-({[(3R)-1-Cyclopentyl-3-piperidinyl]methyl}oxy) phenyl]-4-(phenylcarbonyl)piperazine (E301)	Cyclopentanone	448
1-[4-({[(3R)-1-(Cyclopropylmethyl)-3-piperidinyl] methyl}oxy)phenyl]-4-(phenylcarbonyl)piperazine (E302)	Cyclopropane carboxaldehyde	434

Example 303

4-({4-[4-({[(3*S*)-1-Cyclopentyl-3-piperidinyl]methyl}oxy)phenyl]-1-piperazinyl}carbonyl)benzonitrile (E303)



Step 1: 4-{[4-(4-Hydroxyphenyl)-1-piperazinyl]carbonyl}benzonitrile

4-Cyanobenzoic acid (6.2g, 42.2mmol), 1,3-dicyclohexylcarbodiimide (8.7g, 42.2mmol) and 1-hydroxybenzotriazole hydrate (5.7g, 42.2mmol) were added to a suspension of 4-(1-piperazinyl)phenol (5.0g, 28.1mmol) in dry dichloromethane (50ml). The mixture was stirred at ambient temperature for 2 hours, diluted with dichloromethane and washed with saturated sodium bicarbonate solution. The organic layer was separated, dried under magnesium sulphate and evaporated *in vacuo*. The residue was purified by column chromatography eluting with a mixture of ethyl acetate:hexane (1:1) to give the title compound (2.2g). MS(ES+) m/e 308 $[M+H]^+$.

Step 2: 1,1-Dimethylethyl (3*S*)-3-{[(4-{4-[(4-cyanophenyl)carbonyl]-1-piperazinyl}phenyl)oxy]methyl}-1-piperidinecarboxylate

The title compound was prepared from the product of step 1 and the product of Example 296 Step 2 using the method of Example 295 Step 4. MS(ES+) m/e 505 $[M+H]^+$.

Step 3: 4-{[4-(4-{[(3*S*)-3-Piperidinylmethyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzonitrile

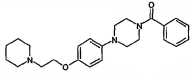
The title compound was prepared from the product of step 2 using the method of Example 295 Step 5. MS(ES+) m/e 405 $[M+H]^+$.

Step 4: 4-({4-[4-({[(3*S*)-1-Cyclopentyl-3-piperidinyl]methyl}oxy)phenyl]-1-piperazinyl}carbonyl)benzonitrile

The title compound were prepared from the product of step 3 and cyclopentanone using the method of Example 295 step 6. MS(ES+) m/e 473 $[M+H]^+$.

Example 304

1-(Phenylcarbonyl)-4-(4-{[2-(1-piperidinyl)ethyl]oxy}phenyl)piperazine (E304)



Step 1: 1-{4-[(2-Bromoethyl)oxy]phenyl}-4-(phenylcarbonyl)piperazine

The product from Example 295 Step 3 (1.0g, 3.55mmol) was dissolved in 2-butanone (20ml), treated with 1,2-dibromoethane (0.46ml, 5.32mmol) and potassium carbonate (0.73g, 5.32mmol) and the resulting mixture was heated under reflux for 18 hours. The reaction mixture was allowed to cool to ambient temperature, diluted with water, made basic by addition of aqueous sodium hydroxide solution (2M) and extracted with ethyl acetate. The ethyl acetate layer was separated, dried under magnesium sulphate and evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with

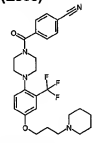
a mixture of ethyl acetate:hexane (1:1) to give the title compound (0.40g). MS(ES+) m/e 390 $[M+H]^+$.

Step 2: 1-(Phenylcarbonyl)-4-(4-{[2-(1-piperidinyl)ethyl]oxy}phenyl)piperazine

The title compound was prepared from the product of step 1 and piperidine using the method of Example 295 Step 4. MS(ES+) m/e 394 $[M+H]^+$.

Example 305

4-({4-[4-{[3-(1-Piperidinyl)propyl]oxy}-2-(trifluoromethyl)phenyl]-1-piperazinyl}carbonyl)benzonitrile (E305)



Step 1: 4-Bromo-3-(trifluoromethyl)phenol

3-(Trifluoromethyl)phenol (1.88ml, 15.4mmol) was dissolved in acetic acid (4ml) and treated with bromine (2.7g, 16.9mmol) dropwise. The resulting mixture was stirred at ambient temperature for 2 hours, poured into water (15ml) and extracted with dichloromethane (x3). The dichloromethane layers were combined, washed with saturated sodium bicarbonate solution, dried under magnesium sulphate and evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with a mixture of hexane:dichloromethane (1:4) to give the title compound (0.73g). ^1H NMR ($CDCl_3$) δ 7.55-7.53 (1H, d), 7.19-7.18 (1H, d), 6.89-6.86 (1H, dd), 5.51 (1H, s).

Step 2: 1-{3-[(4-Bromo-3-(trifluoromethyl)phenyl]oxy}propyl)piperidine

The product from step 1 was dissolved in 2-butanone (30ml), treated with 1-(3-chloropropyl)piperidine hydrochloride (0.72g, 3.63mmol), potassium carbonate (1.17g, 8.48mmol) and sodium iodide (0.15g, 0.91mmol) and heated under reflux for 18 hours. The mixture was allowed to cool to ambient temperature, diluted with ethyl acetate and washed with water. The organic layer was separated, dried under magnesium sulphate and evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with a mixture of .880 ammonia:methanol:dichloromethane (0.5:4.5:95) to give the title compound (0.76g). MS(ES+) m/e 367 $[M+H]^+$.

Step 3: 1,1-Dimethylethyl 4-[4-{[3-(1-piperidinyl)propyl]oxy}-2-(trifluoromethyl)phenyl]-1-piperazinecarboxylate

An oven dried 50ml round bottomed flask was charged with palladium acetate (23mg, 0.10mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (97mg, 0.16mmol) and dry toluene (4ml). The mixture was heated under argon at 100°C for 3 minutes after which a dark purple solution was obtained. The product from step 2 (0.76g, 2.08mmol) in toluene (2ml), 1,1-dimethylethyl 1-piperazinecarboxylate (0.46g, 2.49mmol) in toluene (2ml) and potassium tert-butoxide (0.30g, 3.12mmol) were added and the mixture heated at 100°C

for 5 hours. The reaction mixture was allowed to cool, acidified with acetic acid and passed down an SCX ion exchange column (10g) eluting with methanol followed by a mixture of 0.880 ammonia:methanol (1:9). The basic fractions were combined and evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with a mixture of .880 ammonia/methanol/dichloromethane (0.7:6.3:93) to give the title compound (0.49g). MS(ES+) m/e 472 $[M+H]^+$.

Step 4: 1-[4-{[3-(1-Piperidinyl)propyl]oxy}-2-(trifluoromethyl)phenyl]piperazine

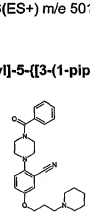
The title compound was prepared from the product of step 3 using the procedure of Example 295 Step 5. MS(ES+) m/e 372 $[M+H]^+$.

Step 5: 4-({4-[4-{[3-(1-Piperidinyl)propyl]oxy}-2-(trifluoromethyl)phenyl]-1-piperazinyl}carbonyl)benzonitrile

4-Cyanobenzoic acid (123mg, 0.84mmol), polymer bound 1,3-dicyclohexylcarbodiimide (1.9mmol/g, 442mg, 0.84mmol) and 1-hydroxybenzotriazole hydrate (113mg, 0.84mmol) were stirred in dry dichloromethane (5ml) for 30 minutes. The product from step 4 (154mg, 0.42mmol) was added and the mixture stirred at ambient temperature for 2 hours. The reaction mixture was diluted with methanol and passed down an SCX ion exchange column (5g) eluting with methanol followed by a mixture of .880 ammonia:methanol (1:9). The basic fractions were combined and evaporated *in vacuo* to give the title compound (0.199g). MS(ES+) m/e 501 $[M+H]^+$.

Example 306

2-[4-(Phenylcarbonyl)-1-piperazinyl]-5-{[3-(1-piperidinyl)propyl]oxy}benzonitrile (E306)



Step 1: 2-Bromo-5-hydroxybenzonitrile

3-Hydroxybenzonitrile (2.0g, 16.8mmol) was dissolved in acetonitrile (20ml) and cooled to –20°C. Tetrafluoroboric acid diethyl ether complex (2.3ml, 16.8mmol) followed by N-bromosuccinimide (3.0g, 16.8mmol) were added and the mixture allowed to warm to ambient temperature. The resulting mixture was stirred for 5 hours, treated with aqueous sodium hydrogen sulfate solution (38%, 10ml) and extracted with methyl 2-methylpropyl ether (x2). The organic extracts were combined, washed with water (x2) and brine, dried under magnesium sulphate and evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with a mixture of methyl 2-methylpropyl ether/dichloromethane (2:98) to give the title compound (1.58g). MS(ES+) m/e 197 $[M-H]^+$.

Step 2: 2-Bromo-5-{[3-(1-piperidinyl)propyl]oxy}benzonitrile

The title compound was prepared from the product of step 1 and 1-(3-chloropropyl)piperidine hydrochloride using the method of Example 305 Step 2. MS(ES+) m/e 324 $[M+H]^+$.

Step 3: 1,1-Dimethylethyl 4-(2-cyano-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinecarboxylate

The title compound was prepared from the product of step 2 and 1,1-dimethylethyl 1-piperazinecarboxylate using the method of Example 305 Step 3. MS(ES+) m/e 429 $[M+H]^+$.

Step 4: 2-(1-Piperazinyl)-5-{[3-(1-piperidinyl)propyl]oxy}benzonitrile

The title compound was prepared from the product of step 3 using the procedure of Example 295 Step 5. MS(ES+) m/e 329 $[M+H]^+$.

Step 5: 2-[4-(Phenylcarbonyl)-1-piperazinyl]-5-{[3-(1-piperidinyl)propyl]oxy}benzonitrile

The title compound was prepared from the product of step 4 and benzoic acid using the procedure of Example 305 Step 5. MS(ES+) m/e 433 $[M+H]^+$.

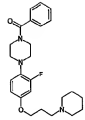
Examples 307-309

The following examples were prepared from the product of Example 306 Step 4 and the appropriate carboxylic acid indicated in table below using the method of Example 305 Step 5.

Example	Carboxylic Acid	MS (ES+) m/e $[M+H]^+$
2-{4-[(4-Cyanophenyl)carbonyl]-1-piperazinyl}-5-{[3-(1-piperidinyl)propyl]oxy}benzonitrile (E307)	4-cyano benzoic acid	458
2-{4-[(4-Fluorophenyl)carbonyl]-1-piperazinyl}-5-{[3-(1-piperidinyl)propyl]oxy}benzonitrile (E308)	4-fluoro benzoic acid	451
5-{[3-(1-Piperidinyl)propyl]oxy}-2-(4-{[4-(1-pyrrolidinylcarbonyl)phenyl]carbonyl}-1-piperazinyl)benzonitrile (E309)	4-(1-pyrrolidinyl carbonyl) benzoic acid (J.Med. Chem., **46**(10), 1845-1857, 2003)	530

Example 310

1-(2-Fluoro-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-4-(phenylcarbonyl)piperazine (E310)



Step 1: 1-{3-[(4-Bromo-3-fluorophenyl)oxy]propyl}piperidine

The title compound was prepared from 4-bromo-3-fluorophenol and 1-(3-chloropropyl)piperidine hydrochloride using the method of Example 305 Step 2. MS(ES+) m/e 317 $[M+H]^+$.

Step 2: 1,1-Dimethylethyl 4-(2-fluoro-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinecarboxylate

The title compound was prepared from the product of step 1 and 1,1-dimethylethyl 1-piperazinecarboxylate using the method of Example 305 Step 3. MS(ES+) m/e 422 $[M+H]^+$.

Step 3: 1-(2-Fluoro-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine

The title compound was prepared from the product of step 2 using the procedure of Example 295 Step 5. MS(ES+) m/e 322 $[M+H]^+$.

Step 4: 1-(2-Fluoro-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-4-(phenylcarbonyl)piperazine

The title compound was prepared from the product of step 3 and benzoic acid using the procedure of Example 305 Step 5. MS(ES+) m/e 426 $[M+H]^+$.

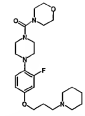
Examples 311-313

The following examples were prepared from the product of Example 310 Step 3 and the appropriate carboxylic acid indicated in the table below using the method of Example 305 Step 5.

Example	Carboxylic Acid	MS (ES+) m/e $[M+H]^+$
4-{[4-(2-Fluoro-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzonitrile (E311)	4-cyanobenzoic acid	451
1-[(4-Fluorophenyl)carbonyl]-4-(2-fluoro-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E312)	4-fluorobenzoic acid	444
1-(2-Fluoro-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-4-{[4-(1-pyrrolidinylcarbonyl)phenyl]carbonyl}piperazine (E313)	4-(1-pyrrolidinyl carbonyl) benzoic acid (J.Med. Chem., **46(10)**, 1845-1857, 2003)	523

Example 314

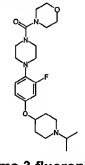
4-{[4-(2-Fluoro-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}morpholine (E314)



The product from Example 310 step 3 (150mg, 0.47mmol) was dissolved in dry dichloromethane (5ml), treated with diethylaminomethyl polystyrene (3.2mmol/g, 294mg, 0.94mmol) and morpholine carbonyl chloride (0.11ml, 0.94mmol) and stirred at ambient temperature under argon for 1 hour. The reaction mixture was diluted with methanol and passed down an SCX ion exchange column (5g) eluting with methanol followed by a mixture of 0.880 ammonia:methanol (1:9). The basic fractions were combined and evaporated *in vacuo*. The residue was purified by column chromatography eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (0.5:4.5:95) to give the title compound (84mg). MS(ES+) m/e 435 $[M+H]^+$.

Example 315

4-{[4-(2-Fluoro-4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)-1-piperazinyl]carbonyl}morpholine (E315)



Step 1: 1,1-Dimethylethyl 4-[(4-bromo-3-fluorophenyl)oxy]-1-piperidinecarboxylate

4-Bromo-3-fluorophenol (5.0g, 26.2mmol) was dissolved in dry tetrahydrofuran (100ml) and treated with 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate (6.3g, 31.4mmol), triphenylphosphine (8.2g, 31.4mmol) and di-t-butylazodicarboxylate (7.2g, 31.4mmol). The resulting mixture was stirred at ambient temperature under argon for 18 hours and the solvent removed *in vacuo*. The residue was triturated with a mixture of ethyl acetate/hexane (1:9), the white solid filtered and the filtrate purified by silica gel chromatography eluting with ethyl acetate:hexane (1:9) to give the title compound (4.67g). MS(ES+) m/e 375 $[M+H]^+$.

Step 2: 4-[(4-Bromo-3-fluorophenyl)oxy]piperidine

The product from step 1 (4.67g, 12.5mmol) was dissolved in dry dichloromethane (30ml), treated with trifluoroacetic acid (20ml) and stirred at ambient temperature for 2 hours. The solvent was removed *in vacuo* and the residue made basic by addition of aqueous sodium hydroxide solution (2M). The resulting mixture was extracted with dichloromethane (x2). The organic layers were combined, washed with brine, dried under magnesium sulphate and concentrated *in vacuo*. The residue was purified by

column chromatography eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (1:9:90) to give the title compound (2.13g). MS(ES+) m/e 275 $[M+H]^+$.

Step 3: 4-[(4-Bromo-3-fluorophenyl)oxy]-1-(1-methylethyl)piperidine

The product from step 2 (2.13g, 7.77mmol) was dissolved in dry dichloromethane (20ml), treated with acetone (0.86ml, 11.7mmol) and acetic acid (2 drops) and stirred for 15 minutes at ambient temperature. Sodium triacetoxyborohydride (2.48g, 11.7mmol) was added and the mixture stirred at ambient temperature under argon for 18 hours. The resulting mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution and brine. The organic layer was dried under magnesium sulphate and evaporated *in vacuo* to give the title compound. MS(ES+) m/e 317 $[M+H]^+$.

Step 4: 1,1-Dimethylethyl 4-(2-fluoro-4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)-1-piperazinecarboxylate

The title compound was prepared from the product of step 3 and 1,1-dimethylethyl 1-piperazinecarboxylate using the method of Example 305 Step 3. MS(ES+) m/e 422 $[M+H]^+$.

Step 5: 1-(2-Fluoro-4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)piperazine

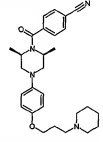
The title compound was prepared from the product of step 4 using the procedure of Example 295 Step 5. MS(ES+) m/e 322 $[M+H]^+$.

Step 6: 4-[[4-(2-Fluoro-4-{[1-(1-methylethyl)-4-piperidinyl]oxy}phenyl)-1-piperazinyl]carbonyl}morpholine

The title compound was prepared from the product step 5 and morpholine carbonyl chloride using the procedure of Example 314. MS(ES+) m/e 435 $[M+H]^+$.

Example 316

4-{[(2*R*,6*S*)-2,6-Dimethyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzonitrile (E316)



Step 1: 1-{3-[(4-Iodophenyl)oxy]propyl}piperidine

1-(3-Chloropropyl)piperidine hydrochloride (9.9g, 50.0mmol), potassium carbonate (17.6g, 127.4mmol) and potassium iodide (1.1g, 6.8mmol) were added to a solution of 4-iodophenol (10g, 45.5mmol) in dimethylformamide (150ml) and the resulting mixture was heated at 90°C for 18 hours. The mixture was allowed to cool to ambient temperature, poured onto water/ice (500ml) and stirred for 10 minutes. The solid was filtered and washed with ice water to give the title compound (13.5g). MS(ES+) m/e 346 $[M+H]^+$.

Step 2: (3*R*,5*S*)-3,5-Dimethyl-1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine

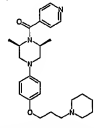
The title compound was prepared from the product of step 1 and (2*R*,6*S*)-2,6-dimethylpiperazine using the procedure of Example 305 Step 3. MS(ES+) m/e 332 $[M+H]^+$.

Step 3: 4-{[(2*R*,6*S*)-2,6-Dimethyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzonitrile

The product from step 2 (249mg, 0.75mmol) was dissolved in dry dichloromethane (5ml), treated with triethylamine (0.21ml, 1.50mmol) and 4-cyanobenzoyl chloride (248mg, 1.50mmol) and the resulting mixture was stirred at ambient temperature under argon for 2 hours. Methanol was added and the mixture passed down an SCX ion exchange column (5g) eluting with methanol followed by a mixture of 0.880 ammonia:methanol (1:9). The basic fractions were combined and evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with ammonia:methanol:dichloromethane (0.5:4.5:95) to give the title compound (158mg). MS(ES+) m/e 461 $[M+H]^+$.

Example 317

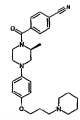
(2*R*,6*S*)-2,6-Dimethyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-(4-pyridinylcarbonyl)piperazine (E317)



4-Pyridinecarboxylic acid (116mg, 0.94mmol) was dissolved in dry dichloromethane (5ml), treated with oxalyl chloride (0.08ml, 0.96mmol) and dimethylformamide (1 drop) and stirred under argon at ambient temperature for 2 hours. The solvent was removed *in vacuo* and the residue azeotroped with toluene. The residue was redissolved in dry dichloromethane (5ml) and treated with the product from Example 316 Step 2 (156mg, 0.47mmol) and triethylamine (0.13ml, 0.94mmol). The resulting mixture was stirred under argon at ambient temperature for 1.5 hours, diluted with methanol and passed down an SCX ion exchange column (5g) eluting with methanol followed by a mixture of .880 ammonia:methanol (1:9). The basic fractions were combined and evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with ammonia:methanol:dichloromethane (0.7:6.3:93) to give the title compound (110mg). MS(ES+) m/e 437 $[M+H]^+$.

Example 318

4-{[(2*S*)-2-Methyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzonitrile (E318)



Step 1: (3S)-3-Methyl-1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine

The title compound was prepared from the product of Example 316 Step 1 and (2*S*)-2-methylpiperazine using the procedure of Example 305 Step 3. MS(ES+) m/e 318 $[M+H]^+$.

Step 2: 4-{[(2S)-2-Methyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzonitrile

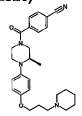
The title compound was prepared from the product of step 1 and 4-cyanobenzoic acid using the procedure of Example 305 Step 5. MS(ES+) m/e 447 $[M+H]^+$.

Examples 319-324

The following compounds were prepared from the product of Example 318 Step 1 with the appropriate carboxylic acid indicated in the table below using the procedure of Example 305 Step 5.

Example	Carboxylic Acid	MS (ES+) m/e $[M+H]^+$
(2*S*)-2-Methyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-{[4-(1-pyrrolidinylcarbonyl)phenyl]carbonyl}piperazine (E319)	4-(1-pyrrolidinylcarbonyl) benzoic acid (J.Med. Chem., **46(10)**, 1845-1857, 2003)	519
(2*S*)-2-Methyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-(4-pyridinylcarbonyl) piperazine (E320)	4-pyridinecarboxylic acid	423
(2*S*)-1-[(4-Fluorophenyl)carbonyl]-2-methyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl) piperazine (E321)	4-fluorobenzoic acid	440
(2*S*)-2-Methyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-(tetrahydro-2*H*-pyran-4-ylcarbonyl)piperazine (E322)	tetrahydro-2*H*-pyran-4-carboxylic acid	430
(2*S*)-2-Methyl-1-{[4-(methylsulfonyl)phenyl]carbonyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E323)	4-(methylsulfonyl) benzoic acid	500
1-(4-{[(2*S*)-2-Methyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}phenyl)ethanone (E324)	4-acetylbenzoic acid	464

Example 325
4-{[(3*R*)-3-Methyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzonitrile (E325)



Step 1: 1,1-Dimethylethyl (3*R*)-3-methyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinecarboxylate

The title compound was prepared from the product of Example 316 Step 1 and 1,1-dimethylethyl (3*R*)-3-methyl-1-piperazinecarboxylate using the method of Example 305 Step 3. MS(ES+) m/e 418 $[M+H]^+$

Step 2: (2*R*)-2-Methyl-1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine

The title compound was prepared from the product of step 1 using the method of Example 295 Step 5. MS(ES+) m/e 318 $[M+H]^+$

Step 3: 4-{[(3*R*)-3-Methyl-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzonitrile

The title compound was prepared from the product of step 2 and 4-cyanobenzoic acid using the procedure of Example 305 Step 5. MS(ES+) m/e 447 $[M+H]^+$.

Examples 326-329

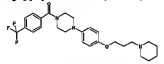
The following compounds were prepared from the product of Example 325 Step 2 with the appropriate carboxylic acid indicated in the table below using the procedure of Example 305 Step 5.

Example	Carboxylic Acid	MS (ES+) m/e $[M+H]^+$
(2*R*)-2-Methyl-1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-4-{[4-(1-pyrrolidinylcarbonyl)phenyl]carbonyl}piperazine (E326)	4-(1-pyrrolidinyl carbonyl) benzoic acid (J.Med. Chem., **46(10)**, 1845-1857, 2003)	519
(2*R*)-2-Methyl-1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-4-(4-pyridinylcarbonyl)piperazine (E327)	4-pyridine carboxylic acid	423
(2*R*)-4-[(4-Fluorophenyl)carbonyl]-2-methyl-1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E328)	4-fluorobenzoic acid	440
(2*R*)-2-Methyl-1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-4-(tetrahydro-2*H*-	tetrahydro-2*H*-pyran-4-	430

pyran-4-ylcarbonyl)piperazine (E329)	carboxylic acid	

Example 330

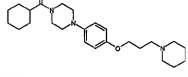
1-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-4-{[4-(trifluoromethyl)phenyl]carbonyl}piperazine (E330)



4-(Trifluoromethyl)phenyl [4-(trifluoromethyl)phenyl]carbonyl carbonate (358 mg, 1 mmol) was added to a stirring solution of 1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (D11) (150 mg, 0.5 mmol) in dichloromethane (20 ml). After 3 hours the mixture was passed through an SCX ion exchange cartridge eluting with methanol and then a mixture of 0.880 ammonia:methanol (1:9). The basic fractions were evaporated and the residue purified on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.5:4.5:95) to furnish the title compound (204 mg, 87%) MS (ES+) m/e 476 $[M+H]^+$.

Example 331

1-(Cyclohexylcarbonyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E331)



Cyclohexanecarbonyl chloride (79 mg, 0.55 mmol) was added to a mixture of 1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (D11) (150 mg, 0.5 mmol) and triethylamine (100 µl, 0.75 mmol) in dichloromethane (5 ml). After 5 hours the solvent was removed by evaporation and the residue purified on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.5:4.5:95) to furnish the title compound (150 mg, 89%) MS (ES+) m/e 414 $[M+H]^+$.

Examples 332-342

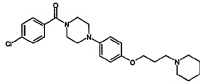
E332 to E342 were prepared from 1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (D11) with the appropriate acid chloride indicated in the table below using the procedure of Example 331

Compound	Acid Chloride	MS (ES+) m/e $[M+H]^+$.
1-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-4-(2-thienylcarbonyl)piperazine (E332)	2-thiophene carbonyl chloride	414
3-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzonitrile (E333)	4-cyanobenzoyl chloride	433
1-{[4-(Methyloxy)phenyl]carbonyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E334)	4-(methyloxy) benzoyl chloride	438

1-(1,3-Benzodioxol-5-ylcarbonyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E335)	1,3-benzodioxole-5-carbonyl chloride	452
1-{[3,5-bis(Trifluoromethyl)phenyl]carbonyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E336)	3,5-bis(trifluoro methyl)benzoyl chloride	544
1-[(3,5-Dichlorophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E337)	3,5-dichlorobenzoyl chloride	477
1-[(4-Bromophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E338)	4-bromobenzoyl chloride	486
1-[(3-Bromophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E339)	3-bromobenzoyl chloride	486
1-[(2,6-Dichlorophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E340)	2,6-dichlorobenzoyl chloride	477
1-(2-Naphthalenylcarbonyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E341)	2-naphthalene carbonyl chloride	458
1-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-4-(3-pyridinylcarbonyl)piperazine (E342)	3-pyridine carbonyl chloride	409

Example 343

1-[(4-Chlorophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E343)



4-Chlorobenzoic acid (192 mg, 1.23 mmol) was treated with *N,N'*-dicyclohexylcarbodiimide (0.25 g, 1.23 mmol) and 1-hydroxybenzotriazole hydrate (165 mg, 1.23 mmol) in dichloromethane (5 ml) after 2 hours 1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (D11) (150 mg, 0.5 mmol) was added and stirring continued for 18 hours. The solvent was removed by evaporation and the residue purified on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.5:4.5:95) to furnish the title compound (198 mg, 91%) MS (ES+) m/e 442 $[M+H]^+$.

Examples 344-374

E344 to E374 were prepared from 1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (D11) with the appropriate carboxylic acid indicated in the table below using the procedure of Example 343.

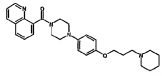
Compound	Acid	MS (ES+) m/e $[M+H]^+$.
1-[(4-Fluorophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E344)	4-Fluorobenzoic acid	426
1-(4-Biphenylylcarbonyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E345)	4-biphenyl carboxylic acid	484
1-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-4-(tetrahydro-2H-pyran-4-ylcarbonyl)piperazine (E346)	tetrahydro-2*H*-pyran-4-carboxylic acid	416
1-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-4-(2-pyridinylcarbonyl)piperazine (E347)	2-pyridine carboxylic acid	409
1-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}isoquinoline (E348)	1-isoquinoline carboxylic acid	459
2-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}quinoline (E349)	2-quinoline carboxylic acid	459
6-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}quinoline (E350)	6-quinoline carboxylic acid	459
1-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-4-(4-pyridinylcarbonyl)piperazine (E351)	4-pyridine carboxylic acid	409
5-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}pyrimidine (E352)	5-pyrimidine carboxylic acid	410
1-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-4-(3-thienylcarbonyl)piperazine (E353)	3-thiophene carboxylic acid	414
Methyl 4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzoate (E354)	4-[(methyloxy) carbonyl] benzoic acid	466
Methyl 3-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzoate (E355)	3-[(methyloxy) carbonyl] benzoic acid	466
1-(Cyclopropylacetyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E356)	cyclopropyl acetic acid	386
1-{[4-Fluoro-2-(trifluoromethyl)phenyl]carbonyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E357)	4-fluoro-2-(trifluoromethyl) benzoic acid	494
1-[(4-Bromo-2-methylphenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E358)	4-bromo-2-methylbenzoic acid	501
1-[(4-Chloro-3-fluorophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E359)	4-chloro-3-fluorobenzoic acid	460
1-{[4-(Methylsulfonyl)phenyl]carbonyl}-4-(4-{[3-(1-	4-	486

piperidinyl)propyl]oxy}phenyl)piperazine (E360)	(methylsulfonyl) benzoic acid	
1-{[2-Chloro-4-(methylsulfonyl)phenyl]carbonyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E361)	2-chloro-4-(methylsulfonyl) benzoic acid	521
1-[(2,4-Difluorophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E362)	2,4-difluoro benzoic acid	444
1-(3-Methylbutanoyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E363)	3-methyl butanoic acid	388
1-[(2,4-Dichlorophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E364)	2,4-dichloro benzoic acid	477
1-[(4-Chloro-2-fluorophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E365)	4-chloro-2-fluorobenzoic acid	461
1-[(4-Fluoro-3-methylphenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E366)	4-fluoro-3-methylbenzoic acid	440
1-[(4-Bromo-2-fluorophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E367)	4-bromo-2-fluorobenzoic acid	505
1-[(3,4-Difluorophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E368)	3,4-difluoro benzoic acid	444
1-[(4-Chloro-3-methylphenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E369)	4-chloro-3-methylbenzoic acid	457
1-[(4-Bromo-3-methylphenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E370)	4-bromo-3-methylbenzoic acid	501
1-[(2-Bromo-4-fluorophenyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E371)	2-bromo-4-fluorobenzoic acid	505
N,N-Dimethyl-3-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}aniline (E372)	3-(dimethyl amino)benzoic acid	451
N,N-Dimethyl-4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}aniline (E373)	4-(dimethyl amino)benzoic acid	451
1-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-4-{[4-(1-pyrrolidinylcarbonyl)phenyl]carbonyl}piperazine (E374)	4-(1-pyrrolidinyl carbonyl)benzoi c acid (Journal of Medicinal	505

	Chemistry (2003), 46(10), 1845-1857)	

Example 375

8-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}quinoline (E375)



A mixture of 8-quinolinecarboxylic acid (U.S. Pat. Appl. Publ., 20020045225, 18 Apr 2002) (173 mg, 1 mmol), polymer bound *N*-cyclohexylcarbodiimide, N-methyl polystyrene HL (200-400 mesh) (526 mg of 1.9 mmol/g resin) and 1-hydroxybenzotriazole hydrate (135 mg, 1 mmol) in dichloromethane (5 ml) was stirred at room temperature for 30 minutes. 1-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)piperazine (D11) (150 mg, 0.5 mmol) was added and stirring continued for 18 hours. The solvent was removed by evaporation and the residue purified on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.5:4.5:95) to furnish the title compound
(93 mg, 41%) MS (ES+) m/e 459 $[M+H]^+$.

Examples 376-431

E376 to E431 were prepared from 1-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (D11) with the appropriate carboxylic acid indicated in the table below using the procedure of Example 375.

Compound	Acid	MS (ES+) m/e $[M+H]^+$.
1-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-4-(3-pyridinylacetyl)piperazine (E377)	3-pyridinylacetic acid	423
6-Methyl-4-{[4-(4-{[3-(1-piperidinyl) propyl]oxy}phenyl)-1-piperazinyl] carbonyl}-2(1H)-pyridinone (E378)	6-methyl-2-oxo-1,2-dihydro-4-pyridinecarboxylic acid	439
1-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-4-(1H-tetrazol-1-ylacetyl)piperazine (E379)	2*H*-tetrazol-2-ylacetic acid	414
1-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-4-{[4-(1H-pyrrol-1-yl)phenyl]carbonyl}piperazine (E380)	4-(1*H*-pyrrol-1-yl)benzoic acid	473
1-Acetyl-4-(4-{[3-(1-piperidinyl)propyl]	Acetic acid	346

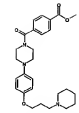
oxy}phenyl)piperazine (E381)		
1-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-4-(1H-1,2,3-triazol-1-ylacetyl)piperazine (E382)	4-(1*H*-1,2,3-triazol-1-yl)benzoic acid	413
1-{2-Oxo-2-[4-(4-{[3-(1-piperidinyl) propyl]oxy}phenyl)-1-piperazinyl]ethyl}-2(1H)-pyridinone (E383)	(2-oxo-1(2*H*)-pyridinyl)acetic acid (Tetrahedron Letters (1998), **39(34)**, 6167-6170)	439
6-{[4-(4-{[3-(1-Piperidinyl)propyl] oxy}phenyl)-1-piperazinyl]carbonyl} quinoxaline (E384)	6-quinoxalinecarboxylic acid	460
5-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-1-piperazinyl]carbonyl} quinoxaline (E385)	5-quinoxalinecarboxylic acid	460
1-(4-{[4-(4-{[3-(1-Piperidinyl)propyl] oxy}phenyl)-1-piperazinyl]carbonyl} phenyl)ethanone (E386)	4-acetylbenzoic acid	450
1-[(Methylsulfonyl)acetyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl) piperazine (E387)	(methylsulfonyl)acetic acid	424
1-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-4-(1,3-thiazol-5-ylcarbonyl)piperazine (E388)	1,3-thiazole-5-carboxylic acid (Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, **(1)**, 132-6; 1976)	415
1-(5-Isothiazolylacetyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl) piperazine (E389)	5-isothiazolylacetic acid (Journal of Medicinal Chemistry (1967), **11(1)**, 70-3.)	429
3-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-1-piperazinyl]carbonyl}-1,2-benzisoxazole (E390)	1,2-benzisoxazole-3-carboxylic acid	449
1-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-4-{[3-(1-pyrrolidinylcarbonyl) phenyl]carbonyl}piperazine (E391)	3-(1-pyrrolidinylcarbonyl) benzoic acid (WO 0304468)	505
2-{[4-(4-{[3-(1-Piperidinyl)propyl] oxy}phenyl)-1-piperazinyl]carbonyl} quinoxaline (E392)	2-quinoxalinecarboxylic acid (Organic Process Research & Development, **6(4)**, 477-481; 2002)	460
4-{[4-(4-{[3-(1-Piperidinyl)propyl] oxy}phenyl)-1-piperazinyl]carbonyl} quinoline (E393)	4-quinolinecarboxylic acid	459
4-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}	6-cyano-3-pyridinecarboxylic	434

phenyl)-1-piperazinyl]carbonyl} cinnoline (E394)	acid (J.Am. Chem.Soc., **68**, 1310-13; 1946)	
3-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}pyrazolo[1,5-a]pyrimidine (E395)	pyrazolo[1,5-*a*]pyrazine-3-carboxylic acid	449
1-[(2-Chloro-6-methyl-4-pyridinyl) carbonyl]-4-(4-{[3-(1-piperidinyl)propyl] oxy}phenyl)piperazine (E396)	2-chloro-6-methyl-4-pyridinecarboxylic acid	458
1-[(1-Methyl-1H-1,2,3-triazol-4-yl)carbonyl]-4-(4-{[3-(1-piperidinyl) propyl]oxy}phenyl)piperazine (E397)	1-methyl-1*H*-1,2,3-triazole-4-carboxylic acid (Journal of Organic Chemistry (1976), **41(6)**, 1041-51)	413
2-{[4-(4-{[3-(1-Piperidinyl)propyl] oxy}phenyl)-1-piperazinyl]carbonyl}-1,8-naphthyridine (E398)	1,8-naphthyridine-2-carboxylic acid	460
5-{[4-(4-{[3-(1-Piperidinyl)propyl] oxy}phenyl)-1-piperazinyl]carbonyl}-1H-indole (E399)	1*H*-indole-5-carboxylic acid	447
2-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-1-piperazinyl]carbonyl}pyrazine (E400)	4-pyrimidinecarboxylic acid	410
3-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-1-piperazinyl]carbonyl} pyrazolo[1,5-a]pyridine (E401)	pyrazolo[1,5-*a*]pyridine-3-carboxylic acid	448
1-(4-{[3-(1-Piperidinyl)propyl] oxy}phenyl)-4-{[4-(1H-tetrazol-1-yl)phenyl]carbonyl}piperazine (E402)	4-(1*H*-tetrazol-1-yl)benzoic acid	476
1-(1-Benzofuran-2-ylcarbonyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl) piperazine (E403)	Benzofuran-2-carboxylic acid	448
1-(3-Isoxazolylcarbonyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl) piperazine (E404)	3-Isoxazolecarboxylic acid	399
5-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-1-piperazinyl]carbonyl}-2,1,3-benzoxadiazole (E405)	2,1,3-Benzoxo-diazole-5-carboxylic acid	450
1-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-4-(3-thienylacetyl)piperazine (E406)	3-Thiopheneacetic acid	428
1-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-4-(1,2,3-thiadiazol-4-	1,2,3-Thiadiazole-4-carboxylic acid	416

ylcarbonyl)piperazine (E407)		
4-{2-Oxo-2-[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]ethyl}benzonitrile (E408)	4-Cyanobenzeneacetic acid (WO 0247762)	447
1-(2,3-Dihydro-1-benzofuran-7-ylcarbonyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E409)	2,3-Dihydrobenzofuran-7-carboxylic acid	450
1-[(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E410)	1,1-dioxohexahydro-1lambda 6 -thiopyran-4-carboxylic acid	464
1-(4-{2-Oxo-2-[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]ethyl}phenyl)ethanone (E411)	4-Acetylphenylacetic acid (Chemical Communications, 2001, **(20)**, 2147-2148)	464
1-{[3,5-bis(Methyloxy)phenyl]carbonyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E412)	3,5-Dimethoxybenzoic acid	468
1-(2-Methyl-2-phenylpropanoyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E413)	2-Methyl-2-phenylpropionic acid	450
1-[(4-Methyl-1,2,3-thiadiazol-5-yl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E414)	4-Methyl-1,2,3-thiadiazole-5-carboxylic acid	430
1-(5-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}-2-thienyl)ethanone (E415)	5-Acetylthiophene-2-carboxylic acid	456
4-{3-Oxo-3-[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]propyl}benzonitrile (E416)	4-Cyanobenzenepropionic acid (US 5726159)	461
3-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}-1,2-benzisothiazole (E417)	1,2-Benzisothiazole-3-carboxylic acid	465
(4-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}-1,3-thiazol-2-yl)acetonitrile (E418)	2-cyanomethyl-thiazole-4-carboxylic acid (Bioorganic and Medicinal Chemistry Letters, **12; 4**; 2002; 561 – 566)	454
3-{2-Oxo-2-[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]ethyl}benzonitrile (E419)	3-Cyanophenylacetic acid (WO 0351797)	447
(4-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}phenyl)acetonitrile (E420)	4-(Cyanomethyl)benzoic acid	447

1-(3,4-Dihydro-2H-chromen-6-ylcarbonyl)-4-(4-{[3-(1-piperidinyl) propyl]oxy}phenyl)piperazine (E421)	2H-1-Benzopyran-6-carboxylic acid, 3,4-dihydro- (Journal of Heterocyclic Chemistry 1994 **31 (2)** 457-79)	464
6-{[4-(4-{[3-(1-Piperidinyl)propyl] oxy}phenyl)-1-piperazinyl]carbonyl}-1,3-benzothiazole (E422)	Benzothiazole-6-carboxylic acid	465
3,5-Difluoro-4-{[4-(4-{[3-(1-piperidinyl) propyl]oxy}phenyl)-1-piperazinyl] carbonyl}benzonitrile (E423)	4-cyano-2,6-difluoro-benzoic acid (US 5914319)	469
1-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-4-[(2,4,6-trifluorophenyl) carbonyl]piperazine (E424)	2,4,6-Trifluorobenzoic acid	462
1-[3-(Methyloxy)propanoyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl) piperazine (E425)	3-Methoxypropionic acid	390
1-[3-(2-Furanyl)propanoyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl) piperazine (E426)	3-(2-Furyl)propionic acid	426
1-[(Methyloxy)acetyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl) piperazine (E427)	Methoxyacetic acid	376
1-[(3,5-Dimethyl-1H-1,2,4-triazol-1-yl)acetyl]-4-(4-{[3-(1-piperidinyl) propyl]oxy}phenyl)piperazine (E428)	(3,5-dimethyl-1H-1,2,4-triazol-1-yl)acetic acid	441
1-[(3,5-Dimethyl-4-isoxazolyl)carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy} phenyl)piperazine (E429)	3,5-Dimethylisoxazole-4-carboxylic acid	427
1-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-4-(tetrahydro-2H-thiopyran-4-ylcarbonyl)piperazine (E430)	Tetrahydrothiopyran-4-carboxylic acid (Helvetica. Chimica. Acta. 1997 **80 (5)** 1528-1554)	432
1-[(1-Oxidotetrahydro-2H-thiopyran-4-yl)carbonyl]-4-(4-{[3-(1-piperidinyl) propyl]oxy}phenyl)piperazine (E431)	2H-Thiopyran-4-carboxylic acid, tetrahydro-, 1-oxide (Arkiv foer Kemi (1966), **26(6)**, 73-7)	448

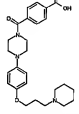
Example 432
Methyl 4-{[4-({[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzoate (E432)



Methyl 4-chlorocarbonylbenzoate (3.6 g, 18.12 mM) was added to a solution of 1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (5g, 16.48 mM) and triethylamine (2.53 ml, 18.12 mM) in dichloromethane (25 ml), and the resulting solution stirred at room temperature for 16 hours. A saturated aqueous solution of sodium bicarbonate (25 ml) was added to the reaction and stirred for 1 hour. The organic phase was separated, washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to afford the title compound (7.46g); MS(ES+) *m/e* 466 $[M+H]^+$.

Example 433

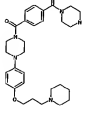
4-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzoic acid (E433)



To a solution of methyl 4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzoate (E432) (6.45 g, 13.86 mM) in a mixture of methanol:water (5:1) (90 ml) was added lithium hydroxide (365 mg, 15.24mM) and the reaction stirred at room temperature for 3 days. Acetic acid (3.17 ml, 55.44 mM) was added and the reaction stirred for an additional 10 minutes. The solvent was evaporated *in vacuo* and the resulting residue dissolved in a mixture of methanol/dichloromethane (1:10) (20ml), and purified using silica gel chromatography eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (2:18:80) to afford the title compound (6.21g); MS (ES+), m/e 452 $[M+H]^+$.

Example 434

1-{[4-(1-Piperazinylcarbonyl)phenyl]carbonyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E434)



Step 1: 1,1-Dimethylethyl 4-[(4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}phenyl)carbonyl]-1-piperazinecarboxylate

N-Cyclohexylcarbodiimide, N-methyl polystyrene HL (200-400 mesh) 1.9 mMol/g (530 mg, 1 mM) was suspended in dichloromethane (10 ml) and treated sequentially with 4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzoic acid (E433) (225 mg, 1 mM), 1-hydroxybenzotriazole hydrate (135 mg, 1 mM) and *tert*-butyl 1-piperazinecarboxylate (93 mg, 0.5 mM) and stirred at room temperature for 16 hours. After filtration, the filtrate was applied to a Mega Bond elute SCX ion exchange column washing sequentially with water and methanol, followed by 0.880 ammonia:methanol (1:10) to elute the crude reaction mixture. Purification by silica gel chromatography eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (0.5:4.5:95) to afford the title product (162 mg); MS (ES+), m/e 620 $[M+H]^+$.

Step 2: 1-[[4-(1-Piperazinylcarbonyl)phenyl]carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine

The title compound was prepared from the product of step 1 (162 mg, 0.26 mM) using the procedure detailed in description D11; MS (ES+), m/e 520 $[M+H]^+$

Examples 435-445

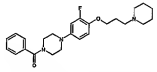
E435 to E445 were prepared from 4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}benzoic acid (E433) with the appropriate amine indicated in the table below using the procedure of Example 434 step 1.

Compound	Amine	MS (ES+) m/e $[M+H]^+$.
1-{[4-(1-Piperidinylcarbonyl)phenyl]carbonyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E435)	Piperidine	519
4-[(4-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}phenyl)carbonyl]morpholine (E436)	Morpholine	521
4-[(4-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy}phenyl)-1-piperazinyl]carbonyl}phenyl)carbonyl] thiomorpholine (E437)	Thiomorpholine	537
1-({4-[(4-Methyl-1-piperidinyl)carbonyl]phenyl} carbonyl)-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl) piperazine (E438)	4-Methyl piperidine	533
N,N-Diethyl-4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy} phenyl)-1-piperazinyl]carbonyl}benzamide (E439)	Diethylamine	507
N,N-Dimethyl-4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy} phenyl)-1-piperazinyl]carbonyl}benzamide (E440)	Dimethylamine 2M Solution in Tetrahydrofuran	479
N-Cyclopentyl-4-{[4-(4-{[3-(1-piperidinyl)propyl]oxy}	Cyclopentyl	519

phenyl)-1-piperazinyl]carbonyl}benzamide (E441)	amine	
1-{[4-(1-Azetidinylcarbonyl)phenyl]carbonyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E442)	Azetidine	491
1-[(4-{[(3S)-3-Fluoro-1-pyrrolidinyl]carbonyl}phenyl) carbonyl]-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl) piperazine (E443)	(S)-3-Fluoro pyrrolidine (WO_9108206)	523
1-{[4-({(2R)-2-[(Methyloxy)methyl]-1-pyrrolidinyl}carbonyl)phenyl]carbonyl}-4-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine (E444)	(R)-2-(Methoxy methyl) pyrrolidine	549
(3R)-1-[(4-{[4-(4-{[3-(1-Piperidinyl)propyl]oxy} phenyl)-1-piperazinyl]carbonyl}phenyl)carbonyl]-3-pyrrolidinol (E445)	(R)-(+)-3-Pyrrolidinol	521

Example 446

1-(3-Fluoro-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-4-(phenylcarbonyl)piperazine (E446)



Step 1: 1-{3-[(4-Bromo-2-fluorophenyl)oxy]propyl}piperidine

2-Fluoro-4-bromophenol (4.20 g, 22 mmol), 1-(3-chloropropyl)piperidine (3.96 g, 20 mmol), potassium carbonate (8.26 g, 60 mmol) and catalytic potassium iodide were heated at reflux for 24 hours in 2-butanone (100 ml). The solids were filtered, washed with acetone and concentrated *in vacuo* to a crude oil. The residue was purified on silica gel eluting with a mixture of ethyl acetate:hexane (0.7:0.3) and then ethyl acetate, to afford the title compound (5.71g, 90%); MS (ES+) m/e 315/317 $[M+H]^+$.

Step 2: 1,1-Dimethylethyl 4-(3-fluoro-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-1-piperazinecarboxylate

The product of step 1 (632 mg, 2mmol), sodium *tert*-butoxide (538 mg, 5.6 mmol), *tert*-butyl 1-piperazinecarboxylate (894mg, 4.8 mmol), tris(dibenzylidineacetone)dipalladium(0) (18 mg, 0.01mmol) and tris(*o*-tolyl)phosphine (24mg, 0.08 mmol) were heated at reflux in toluene (10 ml) for 16 hours. The solution was loaded directly on to a SCX ion exchange resin eluting with methanol and then a mixture of 0.88 ammonia solution:methanol (1:9). The basic fractions were evaporated and the residue purified by silica gel chromatography, eluting with a mixture of .880 ammonia:ethanol:dichloromethane (1:9:190) to afford the title compound (468 mg, 54%); MS (ES+) m/e 422 $[M+H]^+$.

Step 3: 1-(3-Fluoro-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)piperazine

The product of step 2 (468 mg, 1.1 mmol) was dissolved in 1:1 TFA:DCM (10ml) at 0°C and stirred to room temperature over 2 hours. The solution was concentrated *in vacuo*

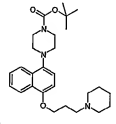
and co-evaporated three times with dichloromethane. The residue was passed through a SCX ion exchange resin eluting with methanol and then a mixture of 0.88 ammonia solution:methanol (1:9). The basic fractions were evaporated and the residue purified by silica gel chromatography, eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichoromethane (1:9:90) to afford the title compound (320 mg, 90%); MS (ES+) m/e 322 $[M+H]^+$.

Step 4: 1-(3-Fluoro-4-{[3-(1-piperidinyl)propyl]oxy}phenyl)-4-(phenylcarbonyl)piperazine

The product of step 3 (320 mg, 1mmol) and triethylamine (140 μL, 1mmol) were dissolved in dichloromethane (5ml), and treated with benzoyl chloride (115 μL, 1 mmol) added. The solution was stirred at room temperature overnight and concentrated *in vacuo* to a crude solid. The solid was purified by silica gel chromatography eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichoromethane (1:9:90) to afford the title compound (354 mg, 83%); MS (ES+) m/e 426 $[M+H]^+$.

Example 447

4-[4-(3-Piperidin-1-yl-propoxy)-naphthalen-1-yl]-piperazine-1-carboxylic acid *tert*-butyl ester (E447)



Step 1: 4-Bromo-naphthalen-1-ol

1-naphthol (1g, 6.94mmol) in acetonitrile (25ml) was treated with N-bromosuccinimide (1.6g, 9.01mmol) and the mixture was stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography eluting with a mixture of hexane: ethyl acetate (0.9:1) to afford the title compound (0.85g, 57%); MS (ES-) m/e 222 $[M-H]^-$.

Step 2: 1-[3-(4-Bromo-naphthalen-1-yl oxy)-propyl]-piperidine

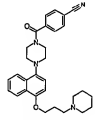
The product from step 1 (0.85g, 3.83mMol) in 2-Butanone (30ml), was treated with 1-(3-Chloro-propyl)-piperidine (0.74g, 4.59mMol), potassium carbonate (1.2g, 9.19mMol), followed by potassium iodide (1.5g, 9.19mMol) and heated under reflux for 6 hours. After cooling to room temperature, the reaction mixture was treated with sodium thiosulphate (1M, 10ml) the product was extracted into ethyl acetate, washed with water (x3), brine (x1), dried over magnesium sulphate and concentrated *In vacuo*. The residue was purified on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.5:4.5:95) to furnish the title compound (0.88g, 68%); MS (ES+) m/e 350 $[M+H]^+$.

Step 3: 4-[4-(3-Piperidin-1-yl-propoxy)-naphthalen-1-yl]-piperazine-1-carboxylic acid *tert*-butyl ester

Palladium bis-*tert*-butyl phosphine (0.033g, 0.064mmol) in *ortho*-xylene (20ml) was treated with the product from step 2 (0.45g, 1.28mmol), piperazine-1-carboxylic acid *tert*-butyl ester (1.47g, 7.67mMol), followed by sodium *tert*-butoxide (0.17g, 1.79mMol) and heated at 120°C for 2 hours. After cooling to room temperature the reaction mixture was diluted with ethyl acetate, washed with water (x3), brine (x1), dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.1:0.9:99) to furnish the title compound (0.40g, 56%); MS (ES+) m/e 454 $[M+H]^+$.

Example 448

4-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-naphthalen-1-yl]-piperazin-1-yl}-methanoyl)-benzonitrile (E448)



Step 1: 1-[4-(3-Piperidin-1-yl-propoxy)-naphthalene-1-yl]-piperazine

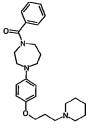
A solution of the product from Examples 447, step 3 (0.40g, 0.89mmol) in anhydrous dichloromethane (5ml) was treated with trifluoroacetic acid (10ml), and stirred at room temperature for 1 hour. The solvent was removed *in vacuo*, dissolved in methanol and applied to a SCX ion exchange column and eluted with methanol and then a mixture of methanol:0.880 ammonia (9:1). The basic fractions were then reduced and the residue was purified on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (1:9:90) to furnish the title compound (0.23g, 73%); MS (ES+) m/e 354 $[M+H]^+$.

Step 2: 4-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-naphthalen-1-yl]-piperazin-1-yl}-methanoyl)-benzonitrile

The title compound was prepared from the product of Step 1 (0.13g, 0.37mmol) and 4-cyanobenzoic acid (0.11g, 0.74mmol) according the procedure detailed in Example 375 (0.17g, 99%); MS (ES+) m/e 483 $[M+H]^+$.

Example 449

1-Phenyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl-[1,4]diazepan-1-yl}-methanone (E449)



Step 1: 4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-[1,4]diazepane-1-carboxylic acid *tert* –butyl ester

A mixture of the product from Example 316, step 1 (1-[3-(4-Iodo-phenoxy)-propyl]-piperidine) (2g, 5.8mMol), [1,4] Diazepane-1-carboxylic acid *tert* –butyl ester (2.7g. 13.9mMol), tris(dibenzylidenacetone) dipalladium(0) (0.03g, 0.03mMol), tri-*ortho*-tolyl-phosphane (0.04g, 0.02mMol) in dioxane (20ml) was heated at reflux for 20 hours. After cooling to room temperature the reaction mixture was diluted with ethyl acetate, washed with water (x3), brine (x1), dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.1:0.9:99) to furnish the title compound (0.61g, 25%); MS (ES+) m/e 418 $[M+H]^+$.

Step 2: 1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-[1,4]diazepane

The title compound was prepared from the product of step 1 (162 mg, 0.26 mM) using the procedure detailed in description D11; MS (ES+) m/e 318 $[M+H]^+$.

Step 3 : 1-Phenyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl-[1,4]diazepan-1-yl}-methanone

The title compound was prepared from the product of step 2 (0.09g, 0.29mmol) and benzoic acid (0.71g, 0.58mmol) using the procedure detailed in Example 375 (0.12g, 95%); MS (ES+) m/e 422 $[M+H]^+$.

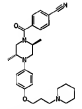
Examples 450-453

E450 to E453 were prepared from Example 449 step 2 with the appropriate carboxylic acids indicated in the table below using the procedure detailed in Example 375.

Compound	Carboxylic Acid	MS (ES+) m/e $[M+H]^+$.
3-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-[1,4] diazepan-1-yl}-methanoyl)-benzonitrile (E450)	3-Cyano-benzoic acid	447
1-Cyclopropyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-[1,4]- diazepan -1-yl}-methanone (E451)	Cyclopropane carboxylic acid	386
1-(4-Fluoro-phenyl)-1-{4-[4-(3-piperidin-yl-propoxy)-phenyl]-[1,4]- diazepan -1-yl}-methanone (E452)	4-Fluoro-benzoic acid	440
1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-[1,4] diazepan -1-yl}-1-thiopheny-2-yl-methanone (E453)	Thiophene-2-carboxylic acid	428

Example 454

4-(1-{(2S, 5R)-2,5-Dimethyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanoyl)-benzonitrile (E454)



Step 1: (2R, 5S)-2,5-Dimethyl-1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine

A mixture of 2,2'-Bis(diphenylphosphino)-1,'-binaphthyl (0.068g, 0.109mmol) and palladium acetate (0.016g, 0.072mmol) in toluene (5ml) were heated to 80°C. To this was added the product from example 316, step 1 (1-[3-(4-iodo-phenoxy)-propyl]-piperidine) (0.5g, 1.45mmol) pre-dissolved in toluene (5ml), (2S, 5R)-2,5-dimethyl-piperazine (0.20g 1.74mmol) predissolved in toluene (5ml), followed by sodium *tert*-butoxide (0.20g, 2.02mmol). The mixture was heated at 100°C for 6 hours. After cooling to room temperature the reaction mixture was diluted with ethyl acetate, washed with water (x3), brine (x1), dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified on silica gel eluting with a mixture of 0.88 ammonia solution:methanol:dichloromethane (0.5:4.5:95) to furnish the title compound (0.98g, 20%); MS (ES+) m/e 332 $[M+H]^+$.

Step 2: 4-(1-{(2S, 5R)-2,5-Dimethyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanoyl)-benzonitrile

The title compound was prepared from the product of step 1 (0.13g, 0.38mmol) and 4-cyanobenzoic acid (0.11g, 0.76mol) using the procedure detailed in Example 375, (0.097g, 57%); MS (ES+) m/e 461 $[M+H]^+$.

Examples 455-458

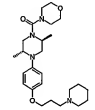
E455 to E458 were prepared from Example 454 step 1 with the appropriate carboxylic acids indicated in the table below using the procedure detailed in Example 375.

Compound	Carboxylic Acid	MS (ES+) m/e $[M+H]^+$.
1-{(2R,5R)-2,5-Dimethyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-1-phenyl-methanone (E455)	Benzoic acid	436
1-{(2R,5R)-2,5-Dimethyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl }-1-pyridin-4-yl-methanone (E456)	Isonicotinic acid	437
1-{(2R,5R)-2,5-Dimethyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-1-[4-(1-pyrrolidin-1-yl-methanoyl)-phenyl]-methanone (E457)	4-(1-Pyrrolidin-1-yl-methanoyl)-benzoic acid (J. Med. Chem., 2003, **46(10)**, 1845-1857)	534
1-{(2R,5R)-2,5-Dimethyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-1-	tetrahydro-pyran-4-carboxylic acid	444

(tetrahydro-pyran-4-yl)-methanone (E458)		

Example 459

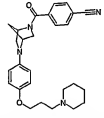
1-{(2R,5R)-2,5-Dimethyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-1-morpholin-4-yl-methanone (E459)



A mixture of the product from Example 454 step 1 (0.20g, 0.60mol), 4-morpholine carbonyl chloride (0.082g, 0.55mol), triethylamine (0.067g, 0.66mol) in dichloromethane (8ml) was stirred at room temperature for 18 hours. The mixture was filtered through am SCX column eluting with methanol followed by 0.880 ammonia solution:methanol (1:9) to afford the title compound (0.18g, 66%); MS (ES+) m/e 445 $[M+H]^+$.

Example 460

4-(1-{5-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-2,5-diaza-bicyclo [2.2.1] hept-2-yl}-methanoyl) benzonitrile (E460)



Step 1: 5-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-2-5-di aza-bicyclo [2.2.1] heptane - carboxylic acid *tert* –butyl ester

The title compound was prepared from example 316, step 1 (1-[3-(4-Iodo-phenoxy)-propyl]-piperidine) (0.25g, 0.72mmol) and 2, 5-Diaza-bicyclo [2.2.1] heptane carboxylic acid *tert* –butyl ester (0.17g 0.87mmol) using the procedure described for example 454, step 1(0.313g, 84%); MS (ES+) m/e 416 $[M+H]^+$.

Step 2: 2-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-2,5-di aza-bicyclo[2.2.1] heptane

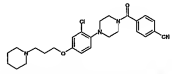
The title compound was prepared from the product of step 1 (0.31g, 0.75mmol) using the procedure detailed in description D11; MS (ES+) m/e 316 $[M+H]^+$.

Step 3: 4-(1-{5-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-2,5-diaza-bicyclo [2.2.1] hept-2-yl}-methanoyl) benzonitrile

The title compound was prepared from the product of step 2 (0.23g, 0.73mmol) and 4-cyanobenzoic acid (0.21g, 1.45mmol) using the procedure detailed in Example 375, (0.27g, 83%); MS (ES+) m/e 445 $[M+H]^+$.

Example 461

4-(1-{4-[2-Chloro-4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanoyl)-benzonitrile (E461)



Step 1: 1-[3-(4-Bromo-3-chloro-phenoxy)-propyl]-piperidine

The title compound was prepared from 1-(3-Chloropropyl)piperidine hydrochloride (2.38g, 12mmol) and 4-bromo-3-chloro-phenol (2.07g, 10mmol) using the procedure detailed in Example 305, step 2, (3.42g); MS (ES+) m/e 333 $[M+H]^+$.

Step 2: 4-[2-Chloro-4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid tert -butyl ester

The title compound was prepared from the product of step 1 (0.6g, 1.8mmol) and 1,1-dimethylethyl 1-piperazinecarboxylate (0.40g, 2.14mmol) using the procedure detailed in Example 305, step 3 (0.46g); MS (ES+) m/e 439 $[M+H]^+$.

Step 3: 1-[2-Chloro-4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine

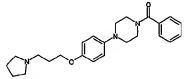
The title compound was prepared from the product of step 2 using the procedure of Example 295 Step 5 (0.240g); MS(ES+) m/e 338 $[M+H]^+$.

Step 4: 4-(1-{4-[2-Chloro-4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanoyl)-benzonitrile

The title compound was prepared from the product of step 3 (0.120g, 0.36mmol) and 4-Cyanobenzoic acid (105mg, 0.712mmol) using the procedure of Example 305 Step 5 (0.130g); MS(ES+) m/e 468 [M+H]

Example 462

1-Phenyl-1-{4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E462)



Step 1: 1-{4-[4-(3-Chloro-propoxy)-phenyl]-piperazin-1-yl}-1-phenyl-methanone

The title compound was prepared from the product of Example 295, Step 3 (4-[4-(phenylcarbonyl)-1-piperazinyl]phenol) (1g, 3.55mmol) and 1-bromo-3-chloro propane (0.67g, 4.25 mmol) using the procedure of Description 9 (1.3g); MS(ES+) m/e 359 [M+H].

Step 2: 1-Phenyl-1-{4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone

The title compound was prepared from the product of step 1 (0.2g, 0.56mmol) and pyrrolidine (0.047g, 0.67mmol) using the procedure of Description 10 (0.15g); MS(ES+) m/e 394 [M+H].

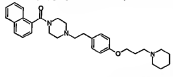
Examples 463-464

E463 to E464 were prepared from Example 462 step 1 with the appropriate amine indicated in the table below using the procedure detailed in Description 10.

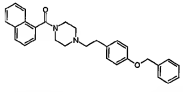
Example	Carboxylic Acid	MS (ES+) m/e $[M+H]^+$.
1-(4-{4-[3-(3,3-Difluoro-pyrrolidin-1-yl)-propoxy]-phenyl}-piperazin-1-yl)-1-phenyl-methanone (E463)	3,3-difluoro-pyrrolidine (Synlett, 1995, **1**, 55-57)	430
1-(4-{4-[3-(4,4-Difluoro-piperidin-1-yl)-propoxy]-phenyl}-piperazin-1-yl)-1-phenyl-methanone (E464)	4,4-Difluoro-piperidine (Tetrahedron, 1977, **33(14)**, 1707-1710)	444

Example 465

1-(1-Naphthalenylcarbonyl)-4-[2-(4-{[3-(1-piperidinyl)propyl]oxy}phenyl)ethyl]piperazine, formate (E465)

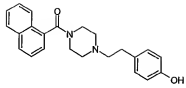


E465a: 1-(1-Naphthalenylcarbonyl)-4-(2-{4-[(phenylmethyl)oxy]phenyl}ethyl) piperazine



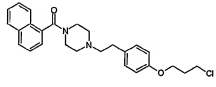
A mixture of 1-(2-bromoethyl)-4-[(phenylmethyl)oxy]benzene (533 mg) and 1-(1-naphthalenylcarbonyl)piperazine (440 mg) was partially dissolved in 1-methyl-2-pyrrolidinone (2 ml) and treated with diisopropylethylamine (0.956 ml). The resulting reaction mixture was heated in a microwave oven at 160°C for a fixed hold time of 12 min. The mixture was partitioned between ethyl acetate and water and the organic phase was washed with water and saturated brine, dried ($MgSO_4$) and evaporated. The residue was loaded on to an SCX-2 SPE cartridge, which was eluted with methanol followed by 2M methanolic ammonia. The methanolic ammonia fraction was evaporated, and the residue was further purified by chromatography on a silica SPE bond elut cartridge eluting with 3% methanol - 1% triethylamine -dichloromethane to give *the title compound* (583 mg). LCMS RT = 2.79 min.

E465b: 4-{2-[4-(1-Naphthalenylcarbonyl)-1-piperazinyl]ethyl}phenol



1-(1-Naphthalenylcarbonyl)-4-(2-{4-[(phenylmethyl)oxy]phenyl}ethyl)piperazine (E465a) (2.33 g) and 20% palladium hydroxide on carbon (800 mg) in ethanol (50 ml) were stirred at room temperature under an atmospheric pressure of hydrogen. After 24 h more palladium catalyst (800 mg) was added and stirring continued for an additional 72 h. The reaction mixture was filtered through celite, washed with ethanol and the filtrate and washings combined and evaporated under vacuum to give *the title compound* (1.84 g). LCMS RT = 2.20 min.

E465c: 1-{2-{4-[(3-Chloropropyl)oxy]phenyl}ethyl)-4-(1-naphthalenylcarbonyl) piperazine



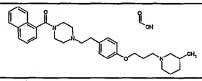
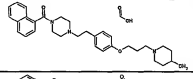
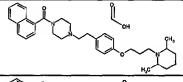
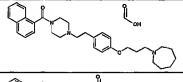
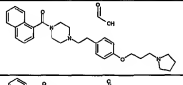
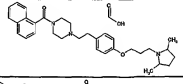
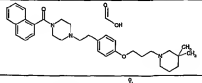
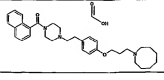
4-{2-[4-(1-Naphthalenylcarbonyl)-1-piperazinyl]ethyl}phenol (E465b) (500 mg), 1-bromo-3-chloropropane (0.165 ml) and potassium carbonate (481 mg) in 2-butanone (25 ml) were heated to reflux for 18 h. More 1-bromo-3-chloropropane (0.165 ml) was added and heating continued for 6 h. The reaction mixture was partitioned between ethyl acetate and water. The aqueous phase was re-extracted with ethyl acetate and the combined organic extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated. The crude material was purified by chromatography on a silica SPE bond elut cartridge eluting with cyclohexane followed by a gradient of 0 – 5 % methanol - dichloromethane - 1% triethylamine to give *the title compound* (582 mg). LCMS RT = 2.67.

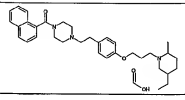
E465d: 1-(1-Naphthalenylcarbonyl)-4-[2-(4-{[3-(1-piperidinyl)propyl]oxy} phenyl)ethyl]piperazine, formate

1-(2-{4-[(3-Chloropropyl)oxy]phenyl}ethyl)-4-(1-naphthalenylcarbonyl)piperazine (E465c) (50 mg), potassium carbonate (95 mg), potassium iodide (95 mg) and piperidine (0.067 ml) in 2-butanone (2 ml) were heated to reflux for 24 h. The reaction mixture was partitioned between dichloromethane and water. The aqueous layer was re-extracted and the combined organic extracts were concentrated and purified by mass directed preparative HPLC to give the title compound (42 mg). LCMS RT = 2.02 min. ES+ve m/z 486 $(M+H)^+$.

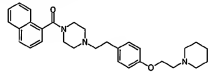
Examples 466 – 474

Examples 466 - 474 were prepared in an array format using the same method described in Example 465d from 1-(2-{4-[(3-chloropropyl)oxy]phenyl}ethyl)-4-(1-naphthalenylcarbonyl)piperazine (0.114 mmol), the appropriate secondary amine (6 eq), potassium carbonate (6 eq) and potassium iodide (5 eq) in 2-butanone (2 ml). The products were purified by mass directed auto-preparative HPLC to provide the compounds as formate salts.

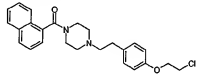
Example	Structure	RT (min)	Mass Ion $(M+H)^+$
466		2.09	500
467		2.07	500
468		2.13	514
469		2.08	500
470		2.00	472
471		2.06	500
472		2.18	514
473		2.19	514

474		2.28	528

Example 475
1-(1-Naphthalenylcarbonyl)-4-[2-(4-{[2-(1-piperidinyl)ethyl]oxy}phenyl)ethyl]piperazine (E475)



E475a: 1-(2-{4-[(2-Chloroethyl)oxy]phenyl}ethyl)-4-(1-naphthalenylcarbonyl)piperazine



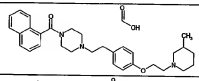
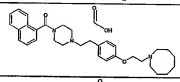
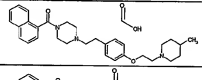
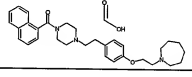
Was prepared from 4-{2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]ethyl}phenol and 1-bromo-2-chloroethane using the same method as described in Example 465c. LCMS RT 2.52 min.

E475b: 1-(1-Naphthalenylcarbonyl)-4-[2-(4-{[2-(1-piperidinyl)ethyl]oxy}phenyl)ethyl]piperazine

1-(2-{4-[(2-Chloroethyl)oxy]phenyl}ethyl)-4-(1-naphthalenylcarbonyl)piperazine (E475a) (23 mg) potassium carbonate (45 mg), potassium iodide (45 mg) and piperidine (0.032 ml) in 2-butanone (2 ml) were heated to reflux for 48 h. The reaction mixture was partitioned between dichloromethane and water. The aqueous layer was re-extracted and the combined organic extracts were concentrated and purified by mass directed preparative HPLC to give the title compound (9.9 mg). LCMS RT = 1.97 min. ES+ve m/z 472 $(M+H)^+$.

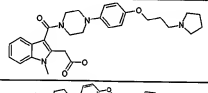
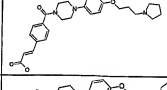
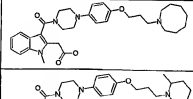
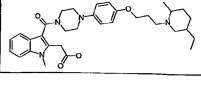
Examples 476 - 479

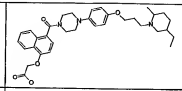
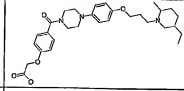
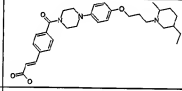
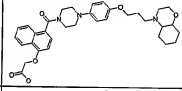
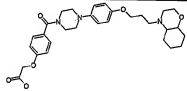
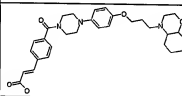
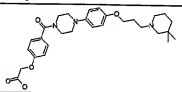
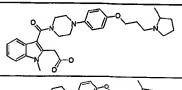
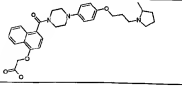
Examples 476 - 479 were prepared in an array format using the same method described in Example 465d from 1-(2-{4-[(2-chloroethyl)oxy]phenyl}ethyl)-4-(1-naphthalenylcarbonyl)piperazine (0.0544 mmol), the appropriate secondary amine (6 eq), potassium carbonate (6 eq) and potassium iodide (5 eq) in 2-butanone (2 ml). The products were purified by mass directed auto-preparative HPLC to provide the compounds as formate salts.

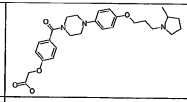
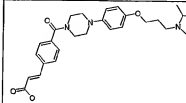
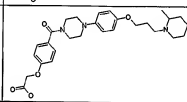
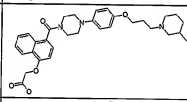
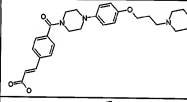
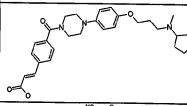
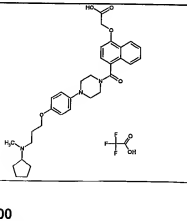
Example	Structure	RT (min)	Mass Ion $(M+H)^+$
476		2.08	486
477		2.13	500
478		2.10	486
479		1.98	486

Examples 480-499

Examples 480-499 were prepared in an analogous manner to the procedure described for Example 62

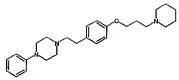
Example	Structure	RT (min)	Mass Ion $(M+H)^+$
480		2.36	505
481		2.24	464
482		2.54	547
483		2.61	561

484		2.59	574
485		2.32	524
486		2.42	520
487		2.43	588
488		2.20	538
489		2.32	534
490		2.24	510
491		2.36	519
492		2.33	532

493		2.07	482
494		2.24	478
495		2.20	496
496		2.50	546
497		2.38	492
498		2.42	492
499		2.40	546

Example 500

1-Phenyl-4-{2-[4-(3-piperidin-1-yl/propoxy)phenyl]ethyl}piperazine trifluoroacetate (E500)

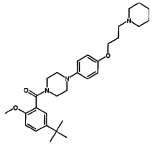


The title compound was prepared from D42 using the procedure described in Example 229d.

RT = 1.86 min, ES+ve m/z 408

Example 501

1-(5-*tert*-Butyl-2-methoxybenzoyl)-4-[4-(3-piperidin-1-ylpropoxy)phenyl]piperazine (E501)

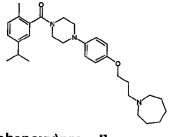


The title compound was prepared from D11 using the procedure described in Example 76c.

RT = 2.61 min, ES+ve m/z 494

Example 502

1-(3-{4-[4-(5-Isopropyl-2-methylbenzoyl)piperazin-1-yl]phenoxy}propyl)azepane (E502)



E502a: 1-[3-(4-Piperazin-1-ylphenoxy)propyl]azepane

The title compound was prepared using an analogous method to that described in Example 76b.

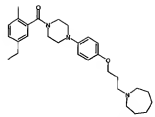
RT = 1.42min, ES+ve m/z 318

E502b: 1-(3-{4-[4-(5-Isopropyl-2-methylbenzoyl)piperazin-1-yl]phenoxy}propyl)azepane

The title compound was prepared from E502a using the procedure described in Example 76c. RT = 2.65 min, ES+ve m/z 478

Example 503

1-(3-{4-[4-(5-Ethyl-2-methylbenzoyl)piperazin-1-yl]phenoxy}propyl)azepane (E503)



The title compound was prepared from E502a using the procedure described in Example 76c.

RT = 2.57 min, ES+ve m/z 464

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Biological Data

A membrane preparation containing histamine H3 receptors may be prepared in accordance with the following procedures:

(i) Generation of histamine H3 cell line

DNA encoding the human histamine H3 gene (Huvar, A. *et al.* (1999) Mol. Pharmacol. **55(6)**, 1101-1107) was cloned into a holding vector, pCDNA3.1 TOPO (InVitrogen) and its cDNA was isolated from this vector by restriction digestion of plasmid DNA with the enzymes BamH1 and Not-1 and ligated into the inducible expression vector pGene (InVitrogen) digested with the same enzymes. The GeneSwitch™ system (a system where in transgene expression is switched off in the absence of an inducer and switched on in the presence of an inducer) was performed as described in US Patent nos: 5,364,791; 5,874,534; and 5,935,934. Ligated DNA was transformed into competent DH5α E. coli host bacterial cells and plated onto Luria Broth (LB) agar containing Zeocin™ (an antibiotic which allows the selection of cells expressing the sh ble gene which is present on pGene and pSwitch) at 50μg ml^{-1}. Colonies containing the re-ligated plasmid were identified by restriction analysis. DNA for transfection into mammalian cells was prepared from 250ml cultures of the host bacterium containing the pGeneH3 plasmid and isolated using a DNA preparation kit (Qiagen Midi-Prep) as per manufacturers guidelines (Qiagen).

CHO K1 cells previously transfected with the pSwitch regulatory plasmid (InVitrogen) were seeded at 2x10e6 cells per T75 flask in Complete Medium, containing Hams F12 (GIBCOBRL, Life Technologies) medium supplemented with 10% v/v dialysed foetal bovine serum, L-glutamine, and hygromycin (100μg ml^{-1}), 24 hours prior to use. Plasmid DNA was transfected into the cells using Lipofectamine plus according to the manufacturers guidelines (InVitrogen). 48 hours post transfection cells were placed into complete medium supplemented with 500μg ml^{-1} Zeocin™.

10-14 days post selection 10nM Mifepristone (InVitrogen), was added to the culture medium to induce the expression of the receptor. 18 hours post induction cells were detached from the flask using ethylenediamine tetra-acetic acid (EDTA; 1:5000; InVitrogen), following several washes with phosphate buffered saline pH 7.4 and resuspended in Sorting Medium containing Minimum Essential Medium (MEM), without phenol red, and supplemented with Earles salts and 3% Foetal Clone II (Hyclone). Approximately 1x 10e7 cells were examined for receptor expression by staining with a rabbit polyclonal antibody, 4a, raised against the N-terminal domain of the histamine H3 receptor, incubated on ice for 60 minutes, followed by two washes in sorting medium. Receptor bound antibody was detected by incubation of the cells for 60 minutes on ice with a goat anti rabbit antibody, conjugated with Alexa 488 fluorescence marker (Molecular Probes). Following two further washes with Sorting Medium, cells were filtered through a 50μm Filcon™ (BD Biosciences) and then analysed on a FACS Vantage SE Flow Cytometer fitted with an Automatic Cell Deposition Unit. Control cells were non-induced cells treated in a similar manner. Positively stained cells were sorted as single cells into 96-well plates, containing Complete Medium containing 500μg ml^{-1} Zeocin™ and allowed to expand before reanalysis for receptor expression via antibody and ligand binding studies. One clone, 3H3, was selected for membrane preparation.

(ii) Membrane preparation from cultured cells

All steps of the protocol are carried out at 4°C and with pre-cooled reagents. The cell pellet is resuspended in 10 volumes of buffer A2 containing 50mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (pH 7.40) supplemented with 10e-4M leupeptin (acetyl-leucyl-leucyl-arginal; Sigma L2884), 25μg/ml bacitracin (Sigma B0125), 1mM ethylenediamine tetra-acetic acid (EDTA), 1mM phenylmethylsulfonyl fluoride (PMSF) and 2x10e-6M pepstain A (Sigma). The cells are then homogenised by 2 x 15 second bursts in a 1 litre glass Waring blender, followed by centrifugation at 500g for 20 minutes. The supernatant is then spun at 48,000g for 30 minutes. The pellet is resuspended in 4 volumes of buffer A2 by vortexing for 5 seconds, followed by homogenisation in a Dounce homogeniser (10-15 strokes). At this point the preparation is aliquoted into polypropylene tubes and stored at -70°C.

(iii) Generation of histamine H1 cell line

The human H1 receptor was cloned using known procedures described in the literature [Biochem. Biophys. Res. Commun. 1994, 201(2), 894]. Chinese hamster ovary cells stably expressing the human H1 receptor were generated according to known procedures described in the literature [Br. J. Pharmacol. 1996, **117**(6), 1071].

Compounds of the invention may be tested for in vitro biological activity in accordance with the following assays:

(I) Histamine H3 binding assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of iodophenpropit (a known histamine H3 antagonist) at a final concentration of 10mM) diluted to the required concentration in 10% DMSO;

(b) 10µl ^{125}I 4-[3-(4-iodophenylmethoxy)propyl]-1H-imidazolium (iodoproxyfan) (Amersham; 1.85MBq/µl or 50µCi/ml; Specific Activity ~2000Ci/mmol) diluted to 200pM in assay buffer (50mM Tris(hydroxymethyl)aminomethane buffer (TRIS) pH 7.4, 0.5mM ethylenediamine tetra-acetic acid (EDTA)) to give 20pM final concentration; and

(c) 80µl bead/membrane mix prepared by suspending Scintillation Proximity Assay (SPA) bead type WGA-PVT at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 80µl which contains 7.5µg protein and 0.25mg bead per well – mixture was pre-mixed at room temperature for 60 minutes on a roller.

The plate is shaken for 5 minutes and then allowed to stand at room temperature for 3-4 hours prior to reading in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data was analysed using a 4-parameter logistic equation.

(II) Histamine H3 functional antagonist assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of guanosine 5'- triphosphate (GTP) (Sigma) as non-specific binding control) diluted to required concentration in assay buffer (20mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM $MgCl_2$, pH7.4 NaOH);

(b) 60µl bead/membrane/GDP mix prepared by suspending wheat germ agglutinin-polyvinyltoluene (WGA-PVT) scintillation proximity assay (SPA) beads at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 60µl which contains 10µg protein and 0.5mg bead per well – mixture is pre-mixed at 4°C for 30 minutes on a roller and just prior to addition to the plate, 10µM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer) is added;

The plate is incubated at room temperature to equilibrate antagonist with receptor/beads by shaking for 30 minutes followed by addition of:

(c) 10µl histamine (Tocris) at a final concentration of 0.3µM; and

(d) 20µl guanosine 5' [γ35-S] thiotriphosphate, triethylamine salt (Amersham; radioactivity concentration = 37kBq/µl or 1mCi/ml; Specific Activity 1160Ci/mmol) diluted to 1.9nM in assay buffer to give 0.38nM final.

The plate is then incubated on a shaker at room temperature for 30 minutes followed by centrifugation for 5 minutes at 1500 rpm. The plate is read between 3 and 6 hours after completion of centrifuge run in a Wallac Microbeta counter on a 1 minute normalised

tritium count protocol. Data is analysed using a 4-parameter logistic equation. Basal activity used as minimum i.e. histamine not added to well.

(III) Histamine H1 functional antagonist assay

Compounds are assayed in a black walled clear bottom 384-well plate with cells seeded at 10000 cells/well. Tyrodes buffer is used throughout (NaCl 145 mM, KCl 2.5 mM, HEPES 10mM, glucose 10mM, $MgCl_2$ 1.2 mM, $CaCl_2$1.5 mM, probenecid 2.5 mM, pH adjusted to 7.40 with NaOH 1.0 M). Each well is treated with 10 µl of a solution of FLUO4AM (10 µM in Tyrodes buffer at pH 7.40) and plates are then incubated for 60 minutes at 37°C. Wells are then washed with Tyrodes buffer using a EMBLA cell washer system, leaving 40µl buffer in each well, and then treated with 10µl of test compound in Tyrodes buffer. Each plate is incubated for 30min to allow equilibration of the test compound with the receptor. Each well is then treated with 10µl of histamine solution in Tyrodes buffer.

Functional antagonism is indicated by a suppression of histamine induced increase in fluorescence, as measured by the FLIPR system (Molecular Devices). By means of concentration effect curves, functional potencies are determined using standard pharmacological mathematical analysis.

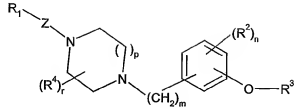
Results

The compounds of Examples E1-260, 263-479 and E499-503 were tested in the histamine H3 functional antagonist assay and exhibited antagonism > 6.5 pK_b. More particularly, the compounds of Examples E1, E3, E10, E12-14, E16-20, E21, E23, E24, E31, E33, E35-37, E40-42, E46-48, E51, E255-256, E258-260, E263, E265-267, E268-271, E273-274, E277-280, E284-288, E290-293, E295, E309, E311, E314-315, E317, E319-329, E331, E333, E342, E344, E346-348, E350, E352, E354-355, E361-363, E368, E374, E378, E380, E384, E386, E389, E391-393, E396-E399, E405, E407, E410-411, E414-415, E420-421, E423-424, E429-431, E434-435, E436-445, E449, E452-453 and E455-459 exhibited antagonism > 8.4 pK_b. Yet more particularly, the compounds of Examples E255, E259, E263, E269, E271, E274, E285-287, E292-293, E333, E344, E346 and E374 exhibited antagonism > 9.0 pK_b.

The compounds of Examples E53-254, E465-479 and E499-503 were tested in the histamine H1 functional antagonist assay and exhibited antagonism > 6.5 pK_b. More particularly, the compounds of Examples E60, E64-65, E67, E70, E84, E87, E91, E93, E95, E98, E100, E108-110, E112, E114-115, E135-136, E162, E171, E188-189, E195, E199, E206-212, E214-219, E224, E229, E231, E235, E242, E244, E466, E468-474 and E500-503 exhibited antagonism > 7.3 pK_b.

CLAIMS:

1. A compound of formula (I):



(I)

wherein:

R^1 represents hydrogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl,- heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl, -heterocyclyl-heterocyclyl,

wherein R^1 may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, $COOR^{15}$, cyano, -C_{1-6} alkyl-cyano, nitro, oxo, trifluoromethyl, trifluoromethoxy, fluoromethoxy, difluoromethoxy, C_{1-6} alkyl (optionally substituted by a $COOR^{15}$ group), C_{2-6} alkenyl (optionally substituted by a $COOR^{15}$ group), C_{2-6} alkynyl (optionally substituted by a $COOR^{15}$ group), C_{1-6} alkoxy (optionally substituted by a $COOR^{15}$ group), pentafluoroethyl, C_{1-6} alkoxy, C_{2-6} alkenoxy, aryl, arylC_{1-6} alkyl, -CO-aryl (optionally substituted by a halogen atom), -CO-heteroaryl, -C_{1-6} alkyl-CO-aryl, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, sulfonyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group -COR^{15}, -$NR^{15}R^{16}$, -$CONR^{15}R^{16}$, -$NR^{15}COR^{16}$, -$NR^{15}SO_2R^{16}$ or -$SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl or together may be fused to form a 5- to 7- membered non-aromatic heterocyclic ring optionally interrupted by an O or S atom and optionally substituted by a halogen, C_{1-6} alkyl or -C_{1-6} alkylC_{1-6} alkoxy group;

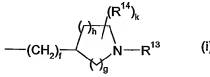
Z represents a bond, CO, -$CON(R^{10})$- or SO_2, such that when R^1 represents hydrogen, Z represents $CONR^{10}$;

p is 1 or 2;

m, n and r independently represent 0, 1 or 2;

R^2 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl, such that when n represents 2, two R^2 groups may instead be linked to form a phenyl ring;

R^4 represents C_{1-6} alkyl, such that when r represents 2, two R^4 groups may instead be linked to form a CH_2, $(CH_2)_2$ or $(CH_2)_3$ group;
R^{10} represents hydrogen or C_{1-6} alkyl, or R^{10}, together with R^1 forms a heterocyclic group;
R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;
R^{11} and R^{12} independently represent C_{1-6} alkyl or C_{3-6} cycloalkyl or together with the nitrogen atom to which they are attached represent an N-linked nitrogen containing heterocyclyl group optionally substituted by one or more R^{17} groups;
R^{13} represents hydrogen, C_{1-6} alkyl, $-C_{1-6}$ alkyl-C_{1-6} alkoxy, C_{3-6} cycloalkyl, $-C_{1-6}$ alkyl-C_{3-6} cycloalkyl, $-C_{1-6}$ alkyl-aryl or heterocyclyl;
R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloalkyl, OH, diC_{1-6} alkylamino, C_{1-6} alkoxy or heterocyclyl;
f and k independently represent 0, 1 or 2;
g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;
with the proviso that when m represents 1, n and r both represent 0 and R^3 represents $-(CH_2)_3$-N-piperidine or $-(CH_2)_3$-N$(ethyl)_2$, R^1-Z represents a group other than methyl, -CO-O-$C(CH_3)_3$ or benzyl;
and with the proviso that when m, n and r all represent 0, p represents 1, R^3 represents $-(CH_2)_3$-N-pyrrolidine or $-(CH_2)_3$-N-piperidine, R^1 represents benzyl, Z represents a group other than a bond;
and with the proviso that when m, n and r all represent 0, p represents 1, R^3 represents–$(CH_2)_3$-N-piperidine, R^1 represents isopropyl, Z represents a group other than a bond;
and with the proviso that when m represents 1, n and r both represent 0, p represents 1, R^3 represents–$(CH_2)_3$-N-piperidine, R^1 represents methyl, isopropyl, aryl or benzyl, Z represents a group other than a bond;
and with the proviso that when m and n both represent 0, R^3 represents $-(CH_2)_3$-N$(ethyl)_2$, p represents 1, r represents 2 and R^1 and R^4 both represent methyl, Z represents a group other than a bond;
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is a compound of formula E1-E503 or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition which comprises the compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

4. A compound as defined in claim 1 or claim 2 for use in therapy.

5. A compound as defined in claim 1 or claim 2 for use in the treatment of neurological diseases or inflammatory diseases of the upper respiratory tract.

6. Use of a compound as defined in claim 1 or claim 2 in the manufacture of a medicament for the treatment of neurological diseases or inflammatory diseases of the upper respiratory tract.

7. A method of treatment of neurological diseases or inflammatory diseases of the upper respiratory tract which comprises administering to a host in need thereof an effective amount of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition for use in the treatment of neurological diseases or inflammatory diseases of the upper respiratory tract which comprises the compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/11423

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/18 C07D317/68 C07D307/85 C07D405/06 C07D243/08
C07D295/22 C07D295/20 C07D295/12 C07D333/38 C07D491/04
C07D403/12 C07D401/12 C07D311/90 C07D487/08 A61K31/496

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 12214 A (ORTHO MCNEIL PHARM INC) 14 February 2002 (2002-02-14) cited in the application Abstract; page 4; claims; examples 7,8,24,26,27,53,88,90,91.	1-8
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-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 2004	03/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Weisbrod, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP 03/11423

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P11/00 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 076925 A (BEAVERS LISA SELSAM; SCHAUS JOHN MEHNERT (US); WATSON BRIAN MORGAN) 3 October 2002 (2002-10-03) Abstract; claims, in particular compounds 102-105, 112-115 of claim 7.	1-8
P,X	WO 03 059341 A (ABBOTT LAB) 24 July 2003 (2003-07-24) Abstract; claims; examples 162,163.	1-8
P,X	WO 03 066604 A (BOEHRINGER INGELHEIM INT; DOERWALD FLORENCIO ZARAGOZA (DK); PETTER) 14 August 2003 (2003-08-14) Abstract; claims; example 147.	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 2004	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Weisbrod, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/11423

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/11423

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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